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2005

document version
Publisher's PDF, also known as Version of record

Risks and Benefits of Experimental Treatments in Oncology

A research into the decision-making of Institutional Review Boards

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This research was carried out within the framework of the incentive program Ethic and Policies, which is supported by the Netherlands Organization for Scientific Research (NWO)

ISBN 90-9019201
NUR 870

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1.1 The assessment of the risk/benefit ratio

In many countries, the law nowadays requires that researchers and doctors need to obtain the informed consent of subjects or patients before involving them in an experiment or initiating a medical plan. In case of medical experiments the informed consent has often to be given by signing a form. The requirement to obtain informed consent is based on the principle of respect for the autonomy of persons. In the analysis by Faden & Beauchamp (1986), informed consent is an autonomous action by a subject or a patient who authorizes a professional to involve the subject in research or to execute a medical plan. The most important condition for giving informed consent is substantial understanding. A patient who is asked to participate in a trial needs to understand the information about the risks, burdens and benefits of the experimental treatment. Medical researchers are only allowed to start a trial if they obtained the approval of an Institutional Review Board (IRB). IRBs have to examine (1) the scientific quality of a trial (its originality, importance, feasibility and methodological soundness), (2) the ratio between the risks and the benefits (RBR) of a trial, and (1) the quality of the information provided to potential research subjects and the quality of the procedures for obtaining consent.

The literature agrees to a great extent on the content and preconditions of informed consent (Appelbaum et al., 1987; Levine, 1988; Faden & Beauchamp, 1986). This is certainly not the case with respect to the assessment of the ratio between the risks and the benefits (RBR) of the trial. “What exactly is an RBR? We all think we know the answer, but do we?” That question led Ernst and Resch to conduct a Medline search (1986 to June 1994). They found 281 papers in which the term ‘risk-benefit ratio’ or more or less synonymous terms were used. Their conclusion was that everyone seemed to take the definition for granted, yet no-one actually provided one (Ernst & Resch 1996). This problem had already been signaled by other authors. Meslin (1993a,b) identified the assessment of the risk/benefit ratio and lack of consultation on the criteria IRBs use in their evaluations as weak links in the evaluation process. Levine – the other author who thoroughly analyzed the problems surrounding the RBR assessment – came to similar conclusions (Levine, 1978, 1986).

Thousands of research protocols must have been approved by IRBs in the last decades. The findings of the above-mentioned authors promt the question how IRBs actually come to conclude that the RBR of a trial is ‘reasonable’, proportional’ or ‘favorable’.

The functioning (Cooke & Tannenbaum, 1977; Gilbert et al. 1989; Hall, 1991; Miller, 1989; While, 1996) and decision making (Goldman & Katz, 1982; Levine, 1984) of Institutional Review Boards (IRBs) has been the subject of limited study. Generally speaking, a great deal of diversity, variability and inconsistency is found when comparing the decision making of different IRBs (Foster, 1995; Foster et al., 1995; Gilbert et al., 1989; Harries et al., 1994, Levine, 1978, 1986). A study of 11 IRBs in the Netherlands showed that most IRBs spend 15 minutes or less discussing a research protocol, including the scientific evaluation (Berghmans et al., 1996; 1997). The most important norms and principles for evaluation are the risk/benefit ratio, scientific issues and the information given to research subjects. If a protocol is found wanting in any of these respects, there is a strong argument for withholding approval. The authors conclude that the protection of research subjects against excessively risky and/or burdensome research is taken very seriously by IRBs. Aspects closely related to protecting the interests of research subjects are the most important in the evaluation process. These include risk/benefit ratio, the way research subjects are recruited, inclusion and exclusion criteria, protecting vulnerable groups of patients, and scientific issues including questions of design and analysis. Although most IRB members set great store by the risk/benefit ratio and scientific issues, they also find them difficult to evaluate. This is also stressed in other studies (Bjune & Gedde-Dahl, 1993; Meslin, 1990; Meslin et al., 1994).

Not only do IRB members have difficulty identifying the relevant risks and benefits of a particular protocol, they also find it difficult to compare those risks and benefits because (1) the nature, extent and the duration of risks and benefits are often uncertain, (2) the nature of the various risks and benefits is very diverse, and (3) all of the risks accrue to the research subjects, while some of the benefits accrue to future patients and/or to medical science. However, although the literature makes clear that IRB members do not find it easy to assess the RBR, next to nothing is known about how the RBR is assessed.

1.2 Background of the research

In our opinion the lack of consensus on the content of, and categories and criteria for evaluating the RBR, causes that IRB evaluations, although usually based on long-term clinical experience, are unavoidably subjective and intuitive. The lack of shared categories and criteria makes it difficult to trace and discuss differences of opinion within an IRB, and thereby reduces the chances that the evaluation of the ratio between risks and benefits will play a prominent role in the final decision regarding the ethical acceptability of the research. This is why we decided to design the research: *The assessment of the risk-benefit ratio of experimental treatments in oncology by Institutional Review Boards as a part of their evaluation of the ethical acceptability of these treatments*.

We had some intuitions about why assessing the RBR is so difficult. These we wanted to examine empirically. Firstly, RBR concerns risks and benefits that have impact on different dimensions of the health or quality of life of the research subject. We inclined to agree with those authors who think that these risks and benefits are incommensurable. The problem of incommensurability is aggravated

because the benefits not only accrue to the research subjects, but also to future patients and medical science. Secondly, the weighing of risks and benefits always takes place within a certain context. Decisions about the RBR of a trial depend on whether there are alternative treatments and on the quality of these alternatives.

1.3 Aims of the research

The aims of the research we developed were:

(1) to provide insight into the factors that play a role in balancing the heterogeneous and incommensurable burdens and benefits of experimental treatments in oncology and that could explain the possible differences in evaluations between members of an IRB;
(2) to provide insight into the impact that judgments on the diverse evaluative dimensions of experimental treatments (scientific importance, soundness, originality, side effects, duration, quantity of tumor remissions, symptom-free period, etc.) have on the final decision about the acceptability of these experiments;
(3) to contribute to increasing the transparency and justifiability of judgments by IRBs about the proportionality of benefits and burdens of experimental treatments in oncology and thereby to enable IRBs to monitor the consistency in their judgments and decisions in regard to different research protocols;
(4) to provide insight into what from an ethical point of view should be the relation between the principle of respect for autonomy – the liberty of research subjects to form, on the basis of their personal preferences and values, their own judgment about the proportionality of benefits and burdens of participating in a research – and the principle of non-maleficience that puts the IRBs under the obligation to make a general judgement of the ethical acceptability of the research;
(5) to contribute to the insight into the feasibility of the legal obligation of IRBs in the Netherlands to determine the proportionality of the ratio between benefits and burdens of medical experiments with humans

1.4 Main research question

Experimental treatments in oncology differ from other experimental treatments in that the risks associated with the treatments are often quite serious. The difficulties in determining the ratio between risks and benefits are therefore more prominent in clinical oncology than in other medical fields. That is why we decided to study the RBR assessment by IRB members and IRBs of clinical cancer trials.

The main research question of this study was:

> *What risks and benefits do IRB members identify in Phase II and III cancer clinical trials, how do they estimate and evaluate these risks and benefits, and what is the relationship of the evaluative dimensions of risks and benefits (e.g. divers physical, psychosocial risks and benefits to participating patients) with the RBR assessment and the ethical acceptability of these experiments? What other factors determine these assessments and can IRBs assess the heterogeneous and incommensurable risks and benefits? And what does it mean when they cannot?*

1.5 Study design

The study we designed is a four-part investigation designed to gain greater insight into RBR assessments of Phase II and Phase III cancer clinical trials. The first stage of the research involved conducting semi-structured interviews with 53 IRB members from IRBs at six research hospitals and specialized cancer centers in the Netherlands to determine their attitudes, beliefs and experiences in evaluating the RBR of Phase II and III cancer clinical trials in general. In the second stage of the study, 43 and 41 of these IRB members evaluated two protocols (a Phase II and a Phase III clinical trial) by means of a questionnaire. In the third stage, in-depth interviews were conducted with 35 of the IRB members from the second stage about the protocol evaluations that they had carried out in stage two. The final stage of the study involved observation and analysis of the meetings of the full IRBs of two of the participating hospitals, during which the two protocols evaluated in stages two/three were discussed. Part of the results from the second through fourth stages of this investigation are not described in this report, but will be reported in subsequent papers.

One of the most important decisions we made in designing our study was to work with closed questions as well as open-ended questions in the questionnaires and interviews. Churchill et al. (2003) who also interviewed IRB members about how they assess benefits, used only open-ended questions (e.g. an open-ended question about benefit: "There are several kinds of benefits that might be associated with research. What kinds of benefits does your IRB look for when reviewing a study?"). According to Churchill et al., the advantage of this approach is that the respondents' answers are not restricted to choices pre-determined by the investigator. This was particularly important to them, as they wanted to know what people would say without any prompting. By providing IRB members also with closed questions, we hoped to attain two other goals. First, to make the data obtained by the questionnaires and the interviews comparable and thus to be able to analyse the data in a quantitative way. Second, to provide the IRB members with a 'language' in which they could articulate their implicit decisions and what they find relevant and not relevant to include in their assessment.

1.6 Content of this report

In Chapter 2 the conceptual model that has been developed for the study will be described. In Chapters 3 to 6 the empirical and empirical-ethical studies will be presented. The article in Chapter 3 has been published; the others are under primary or secondary review. Chapter 7 summarizes the main results of the study and discusses these in light of the conceptual model.

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2 Conceptual framework and assessment model

In this chapter the conceptual framework and the assessment model developed for the research will be described. The operationalization of the concepts and the different blocks of the model are described more extensively in the Method and Subjects sections of the various articles (see Chapters 3-6) and in the manuscripts that are in preparation.

2.1 The conceptual frameworks and assessment models of Katz, Levine and Meslin

The most important contributions to the study of RBR assessment of medical research involving humans are without doubt those of Levine and Meslin (Levine, 1978, 1986; Levine et al., 1884; Meslin, 1989; Meslin, 1990; Meslin, 1993a,b; Meslin et al. 1994). Levine (1986) developed a set of categories to distinguish between risks and benefits for participating patients, for future patients and for society at large (scientific progress). These categories have been further refined by distinguishing between different kinds or dimensions of risks and benefits for participating patients (e.g. physical, psychological, social). Meslin (1989) devoted special attention to the process of risk assessment by IRB members. He identified three 'decision-making processes' in risk assessment: identification, estimation and evaluation of risks. Risk consists of an estimation of the chance and the magnitude of the possible harm. Chance can be further divided into an objective and a subjective probability estimation. This distinction is necessary because often there are not enough empirical data available, or the persons called upon to evaluate these data are prejudiced. Also, subjective considerations would influence the risk assessment, because values that were attributed to the objective estimations of the risk of harm determine what is a considered to be a risk, and whether it can– after it is assessed as harm –be evaluated as acceptable or not acceptable. This view of the process of risk assessment forms the basis of the four-cell matrix that Meslin has made to improve risk assessments by IRBs (see Table 2.1).

Table 2.1: *A proposed matrix for risk judgements in medical research(Meslin, 1989)*

	CONSIDERATIONS	
	Objective	***Subjective***
EXPRESSION OF RISK		
Probability of harm	Objective probability of harm	Subjective probability of harm
Magnitude of harm	Objective magnitude	Subjective magnitude

In designing our research on how IRB members make their RBR assessments, we made extensive use of Katz's and Levine's taxonomies of the kinds of risks and benefits and Meslin's model of the process of risk assessments. However, the aim of

these authors in developing these taxonomies and models was not to provide a framework for describing the actual process of risk/benefit assessment by IRBs; they hoped that IRBs, by using these instruments, would improve the quality of their assessments. We believed that these taxonomies and models were not alien to the manner in which IRB members actually come to their RBR assessment. Meslin acknowledges this when he said that IRBs already apply a sort of risk assessment, because IRBs ask researchers to describe what kind of risks and benefits to human subjects will result from participation in a trial (Meslin, 1989).

2.1 Supplements and modifications

In order to be able to investigate the whole assessment and evaluation process that – as we assumed – takes place during the RBR assessment of medical research protocols, it is first necessary to describe – as far as possible – all stages of the process. Secondly, it is necessary that all the factors that influence – as we expected – the assessment also are incorporated in the model. The taxonomies of risks and benefits developed by Katz and Levine (1984) and Levine (1986), elements from Meslin's risk assessment model and his four-cell matrix to improve the risk assessments of (Meslin, 1989, 1990), were the starting-points for the conceptual model we developed (see Figure 2.1). These starting-points were complemented with insights from the theory of interactive evaluation and decision making of Straver and Van Luijn (Van Luijn & Straver, 1994; Van Luijn, 1996), insights from the descriptive approach of psychological decision making in cognitive psychology (see a.o. Koele & Van der Pligt, 1993; Harte & Koele, 1997) and insights from the empirical literature on the RBR assessment by IRBs and IRB members of human subject research.

Theory of interactive evaluation and decision making

The theory of interactive evaluation and decision making integrates the theory of coping with stressful life events (Lazarus & Folkman, 1984; 1991) with that of decision making under stress (Janis and Mann, 1977). In the theory of coping with stressful life events there is (preceding coping as such) a judging and evaluative process that consists of two parts: a primary and a secondary appraisal. The primary appraisal refers to the perception, judgment and evaluation of an event as stressful with respect to the well-being of the person. The secondary appraisal refers to the question whether something can be done to take away the threat. The theory about decision making under stress (Janis and Mann, 1977) deals with the strategies people choose to come to a decision when emotional aspects and/or time pressure play a role. In the theory of interactive evaluation and decision making both theories are integrated. Hereby the decision-making strategies in the theory of Janis and Mann are placed in a context in which person-related and context-related factors determine the judgment, evaluation and decision-making process. This approach was used in this study as a general decision-making theory to understand and investigate the RBR assessment by IRB members of clinical trial protocols. It is complemented with the insights of the descriptive approach of decision making in cognitive psychology.

Descriptive approach of decision making

Decision-making behavior can be studied from different perspectives. The most important distinction is that between normative and descriptive approaches (Koele & Van der Pligt, 1993; Harte & Koele, 1997). In the normative approaches the decision problem is well defined and there are axiomatic theories that prescribe which decision a rational person should make to maximize the possibility to reach a certain goal. The descriptive approach is not interested in what rational subjects should do, but what subjects in reality do. The aim is instead to understand and to explain how individuals cope with available information to come to a decision. The descriptive approach considers individual differences in decision making not as deviations from normal behavior, but as relevant conceptual differences that can be explained by factors that influence the decision-making process, such as motivational, cognitive and emotional factors, time-related, and context factors, and factors that correlate with the complexity of the task that must be performed.

2.2 Conceptual framework and assessment model of the present study

The conceptual model of this study was developed on the basis of the above-mentioned conceptual frameworks and theoretical models, and by drawing insights from the empirical studies into the RBR assessment by IRBs and IRB members. As can be seen in Figure 2.1, the model identifies several stages within the decision-making process and several factors which may influence the process. Not visible in Figure 2.1 is that we conceptualized a separate process of identification, estimation and evaluation of the risks and of the benefits of the research for the participating patients. The same is true for the risks and benefits of the research for future patients and medical science (or society). Although theoretically there must be six separate

processes, in reality there are only four, because normally there are no research risks for future patients and/or society.[1] We expected that these four processes first take place separately for: (1) the risks of the research for the participating patients, (2) the benefits of the research for the participating patients, (3) the benefits of the research for future patients, and (4) the benefits of the research for medical science (or society). In a second stage the outcomes of those four evaluation processes, namely four evaluations, will be weighed against each other.

In the case of Phase III studies not only the ratio between the risks and benefits of the experimental arm must be evaluated, but also the risks and benefits of the control arm. This means that the above-described process actually will be repeated. The goal of the repetition is to determine whether the RBR of the experimental arm is not too different from the RBR of the control arm with respect to the risks and benefits to the participating patients. When both arms differ a great deal in this respect, it is unethical to let the study take place. Although the above-described process takes place again, there are not three but only two different identification, estimation, and evaluation processes of the risks and benefits of the control arm, while it is not necessary to weigh the risks and benefits for future patients and/or society. The control arm consists most of the time of the standard treatment already evaluated when the standard treatment was itself experimental.

In the rest of this section the different concepts of the model are described.

[1] Levine (1986) mentioned as possible risks of research for society for example: premature publication of research results that unnecessarily can cause panic or the opposite create hope (think about AIDS research). The escape of bacteria from a laboratory that possibly can cause an epidemic is another example.

Judgment and evaluation

As mentioned above, a judging and evaluative process that consists of two parts, a primary appraisal and a secondary appraisal, will precede the coping (=decision making) in the theory of coping with stressful life events. The primary appraisal refers to the perception, judgment and evaluation of an event as stressful with respect to the well-being of the person; the secondary appraisal to the question whether something can be done to take away the threat. Both appraisals can be filled out with the three stages that are distinguished in the model of risk assessment, namely: (1) risk identification, (2) risk estimation, and (3) risk evaluation. As can been seen in Figure 2.1, in our conceptual model these stages not only refer to the risks – as in the risk-assessment approach – but also to the benefits. Determining the risks consists of the identification and estimation of the inconvenience, of the likelihood, severity, duration, reversibility and amenability to treatment of the physical risks (i.e. the toxicity), and of the likelihood, severity and duration of psychosocial risks (or distress). Determining the benefits consists of the identification and estimation of the likelihood, duration and importance of the benefits to the research subjects and of the importance of the research to future patients and medical science. The risk evaluation (and benefit evaluation) is done for the risks and the benefits separately as well as in relation to each other (weighing the risks and benefits), as can been seen in the two instances in Figure 2.1 where evaluation of risks and benefits takes place.

Decision making

Decision making itself consists of problem-focused and of the so-called emotion-focused strategies, as can be seen in Figure 2.1. The problem-focused strategies are for instance rational weighing of risks and benefits and information-search processes. Emotion-focused strategies or emotion-regulation processes are strategies such as mental anticipation, denial or wishful thinking. These emotion-regulation processes are distinguished in the theory of coping with stressful life events (Lazarus & Folkman, 1984, 1991) and in the theory of decision making under conflict or stress (Janis & Mann, 1977). We expected (part of) these latter processes also to take place when IRBs and IRB members need to assess the RBR of clinical cancer trials, especially when it is not easy to decide on the ratio between the risks and the benefits of the trial.

Although approving or rejecting a research protocol is different from important individual decisions with consequences for a person's life such as decisions to divorce, to have children or to change career (examples in the theory of decision making under stress), we do think that our conceptual model can contribute to the clarification of the RBR assessment by IRBs and IRB members. The main reason is that recent developments in the descriptive approach of decision making in cognitive psychology underline the importance of emotional factors on decision making in general (Koele & Van der Pligt, 1993; Harte & Koele, 1997).

Determining factors

The factors that influence decision making in the theory of interactive evaluation and decision making and in the descriptive approach of decision making are person-related and context-related factors, such as personal beliefs, problem-

solving skills, social skills, social support, material resources, extent to which the threat is felt, motivational, cognitive and emotional factors, time-related factors, and factors that correlate with the complexity of the task. The factors present in the theoretical and empirical literature on the RBR assessment which we used to fill out the determining blocks in the model, will be mentioned below. More information about the relationship between these factors and the RBR assessment can be found in a separate review of the literature (Van Luijn, forthcoming).[2] Research into the RBR assessment by IRB members and IRBs of research protocols is limited. Sometimes the literature is already quite old; often the research is qualitative with a limited number of respondents. This means that the literature is mainly used to develop an indicative conceptual model.

The factors determining the RBR assessment by IRB members and IRBs of research protocols mentioned in the theoretical and empirical literature are: the identification, estimation and evaluation of risks and benefits to participating patients, future patients and medical science (Meslin, 1989, Levine, 1986, Shannon & Ockene, 1985) and person- and context-related factors. Person-related factors determining the decision making and RBR assessment are: the professional status and sociodemograhic characteristics of IRB members (Berghmans et al., 1996, 1997), the competence of IRB members (Schwartz, 1983; Williams, 1984; Meslin, 1989), (un)clarity about the risk/benefit ratio concept and about legal regulations or lack of rules (Levine, 1986; Meslin, 1989; Williams, 1984), IRB members' judgment about the relevance of scientific and risk/benefit issues for the RBR assessment (Berghmans et al. 1996, 1997), IRB members' focus on rights, rather than well-being of participating patients (Williams, 1984), and IRB members' beliefs on the value of life (Tiemstra, 1995). Context-related factors are: the available information in protocols (Meslin, 1989), available alternative treatments (Meslin, 1989), the composition of the IRB (Williams 1984; Meslin, 1990; Holm, 1992; Darvall, 1995; Berghmans et al., 1996), the quality of the researcher or the fact that the researcher is known, and the presence of researchers during committee meetings (Shannon & Ockene, 1985). In this chapter we do not describe how these factors are related to the RBR assessment by IRB members or IRBs of research protocols. This can be found in the review of the literature, as said earlier and also partly in the separate articles.

[2] Van Luijn, H.E.M. (2005). De bepaling van de risk benefit ratio van medisch experimenteel onderzoek door medisch-ethische toetsingscommissies. Een literatuuroverzicht. [The assessment of the risk benefit ratio of medical experimental research by Institutional Review Boards (will be published as a separate report).

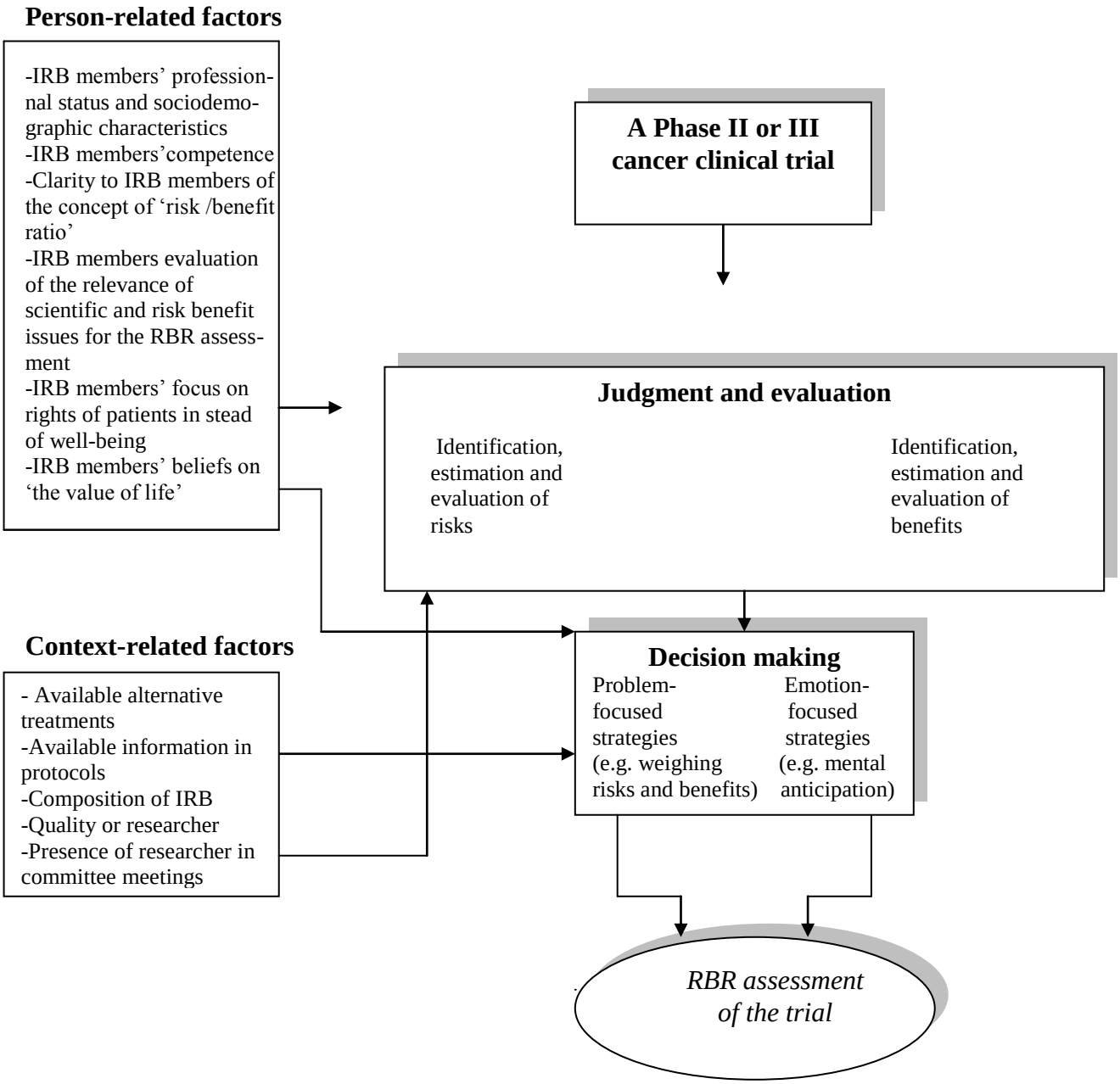

Figure 2.1: *Judgment, evaluation and decision making by IRB members on the risk/benefit ratio (RBR) assessment of Phase II and III cancer clinical trials*

This model is translated into the different instruments that were used in this study (semi-structured interviews, questionnaire, extended interviews and observation). The operationalization of the different blocks of the model can be found, as noted above, in the Method & Subjects sections of the articles.

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*3 Assessment of the risk/benefit ratio of phase II cancer clinical trials by Institutional Review Board (IRB) members **

Summary

Background: This study examined the assessment of risk/benefit ratios for phase II cancer clinical trials by Institutional Review Board (IRB) members. Subjects and Methods: Semi-structured interviews were conducted with 53 members of IRBs from six research hospitals and specialized cancer centers in the Netherlands. Results: While the toxicity and side-effects of treatment were most often identified as risks associated with participating in a phase II trial, approximately two-thirds of IRB members also cited psychosocial and/or quality-of-life risks. Conversely, 68% of the respondents identified psychosocial benefits of trial participation, while 25% cited treatment effectiveness as a possible benefit. Between one-quarter and two-thirds of respondents indicated that trial protocols provide insufficient information about the likelihood, magnitude and duration of both risks and benefits. Between 15% and 34% of IRB members reported feeling less than fully competent to evaluate various aspects of phase II protocols (e.g., originality and feasibility of the study, adequacy of the methods and analysis procedures, etc.). This was particularly the case for non-physician IRB members. Few IRB members reported weighing risks and benefits in a systematic manner, but rather relied on global impressions or preferred to leave such matters to the IRB as a whole or to their patients.
Conclusions: A substantial minority of IRB members believes that trial protocols provide too little information relevant to evaluating various cost/benefit and scientific issues, and feels less than fully competent in carrying out such evaluations. IRB members are more likely to identify psychosocial benefits than physical health benefits that may accrue to patients participating in phase II trials.

3.1 Introduction

Despite the importance of the work of Institutional Review Boards in the ethical conduct of human research, the process of decision-making by IRB members has been the subject of only limited study. (Cooke & Tannenbaum, 1977; Gilbert et al., 1989; Hall, 1991; Miller, 1989; While, 1996; Goldman & Katz, 1982; Levine et al., 1984; Foster et al., 1995; Harries et al., 1994). While variability in both the process and outcome of decisions made by IRBs has been documented in the U.S. (Goldman & Katz, 1982) and elsewhere (Harries et al., 1994), there is a general consensus that the assessment of risk and benefit is an essential part of the protocol review process. A study of 11 IRBs in the Netherlands ranked risk/benefit ratio, scientific validity and the adequacy of patient information as the most important factors considered by IRB members (Berghmans et al., 1996). The authors of this study concluded that the protection of research subjects against excessively risky and/or burdensome research

* H.E.M. van Luijn, A.W. Musschenga, R.B. Keus, W.M. Robinson & N.K. Aaronson (2002). *Annals of Oncology*, *13* (8), 1307-1313.

is taken very seriously by IRBs, but they did not describe the process of review used in evaluating trial protocols. Although most IRB members set great store by the risk/benefit ratio and scientific issues, they also find them difficult to evaluate (Berghmans et al., 1996; Bjune & Gedde-Dahl, 1993; Meslin, 1990; Meslin et al., 1994). This is especially true for non-medical IRB members (Berghmans et al., 1996). The assessment of the risk/benefit ratio and lack of consensus on the criteria IRBs use in their evaluations have been identified as weak links in the evaluation process (Meslin, 1993a,b).

The study reported here is the first of a four-part investigation designed to gain greater insight into RBR assessments of phase II and phase III cancer clinical trials. This first stage of the research involved conducting semi-structured interviews with IRB members to determine their attitudes, beliefs and experiences in evaluating the RBR of phase II cancer clinical trials, in general (Van Luijn, 2000). In the second stage of the study, IRB members were asked to evaluate two protocols (a phase II and a phase III clinical trial) by means of a questionnaire. In the third stage, in-depth interviews were conducted with the IRB members about the protocol evaluations that they had carried out in stage two. The final stage of the study involved observation and analysis of the meetings of the full IRBs of two of the participating hospitals during which the two protocols evaluated in stages two/three were discussed. The results from the second through fourth stages of this investigation will be reported in subsequent papers.

In the first stage of this research, we evaluated four aspects of the risk/benefit assessment process: (1) identification of the risks and benefits of phase II cancer clinical trial protocols, (2) estimation of the amount of information needed to make a

risk/benefit assessment and whether such information is typically available in phase II clinical trial protocols, (3) self-reported competence of IRB members to make risk/benefit assessments, and (4) evaluation of specific risks and benefits for patients participating in phase II clinical trials, for future cancer patients, and for medical science.

3.2 Subjects and methods

Study subjects

IRB members from 6 hospitals in the Netherlands were invited to participate in the study, including the academic hospitals of the universities of Utrecht, Rotterdam, and Leiden, the Vrije Universiteit in Amsterdam, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in Amsterdam, and the Daniel den Hoed Cancer Center in Rotterdam. Sixty-five IRB members were originally approached, of whom 53 (81%) agreed to participate. The remaining twelve individuals declined to participate due to the time-consuming nature of the research. The participating IRB members included medical specialists (41%), family physicians (8%), nurses (15%) and other disciplines (36%), including four pharmacists, two ethicists, two social scientists, one statistician, one attorney and others (17%). The age of the participants

ranged from 28 to 69 years. The majority (64%) was male. Nine percent had been an IRB member for less than 1 year, 47% for 1-4 years, and 44% for 4 years or longer.

Study measures – the semi-structured interview

The semi-structured interviews, including a combination of open- and closed-ended questions, focused on the identification, estimation and evaluation of the risks and benefits associated with phase II clinical trials. On average, the interviews took approximately 1 hour to complete.

Identification of risks and benefits

A series of open-ended questions was asked about the *identification of risks and benefits* associated with phase II studies: (1) "How do you determine what risks and benefits to participating patients are associated with phase II studies?" (2) "What type of risks and benefits (to participating patients) do you identify in phase II studies? and (3) "What type of benefits do you identify in phase II studies for future patients and for medical science?"

Estimation of risks and benefits

Two types of questions with closed-ended response categories were asked about the *estimation of risks and benefits* associated with phase II studies: (1) on the adequacy of information contained in trial protocols for evaluating risk/benefit issues; and (2) on the perceived competence of IRB members to evaluate scientific and risk/benefit ratio issues. The adequacy of the information contained in trial protocols was assessed with the question: "In general, do you think that you are given enough information (empirical data) in phase II protocols to judge the

following issues?" Responses were scored on a 4-point Likert-type scale, ranging from 'more than enough' to 'very insufficient.' The specific issues addressed are listed in Table 3.1.

A modified version of a questionnaire developed at the Institute of Health Ethics in Maastricht (the Netherlands) was used to assess the perceived competence of IRB members in protocol evaluation. Respondents were asked: "In general, how easy or difficult do you find it to evaluate the following risk/benefit and scientific issues of phase II cancer clinical trial protocols? In other words, how competent do you feel to evaluate these issues?" The specific issues addressed are listed in Table 3.2. Response categories ranged on a 5-point Likert-type scale from 'very easy' to 'very difficult'.

Table 3.1: *Perceived adequacy of information contained in phase II protocols (N=53)*

	Percent rated as (very) insufficient
The type of benefits to the patient	8%
The likelihood of benefits to the patient	26%
The magnitude of the benefits to the patient	36%
The duration of the benefits to the patient	46%
The type of risks to the patient	19%
The likelihood of risks to the patient	44%
The seriousness of the risks to the patient	36%
The duration of the risks to the patient	60%
The reversibility of the risks to the patient	36%
The importance of the research for future patients	11%
The importance of the research for science	10%

Table 3.2: *Perceived competence to evaluate risk/benefit and scientific issues of phase II protocols (N=53)*

	Percent rated as (very) difficult
Risks/benefit issues	
The burden, inconvenience and risks to participating patients	30%

The toxicity and side-effects of treatments	23%
The degree of invasiveness of the treatments	15%
The benefits to participating patients	34%
The benefits to future patients	34%
The benefits to medical science	21%
Scientific issues	
The aims of the trial	8%
New insights provided by the trial	15%
The originality of the trial	40%
The feasibility of the trial	34%
The scientific methodology of the trial	30%
The scientific relevance of the study	6%
The relationship of the trial to earlier studies	32%
How the data are to be analyzed	42%

Evaluation of risks and benefits

Two related, open-ended questions were posed to determine how IRB members *evaluate the risks and benefits* of phase II clinical trials: (1) "How do you judge the acceptability of risks in relation to the benefits to participating patients, future patients and society? This was sometimes followed up with: "In other words, how do you weigh risks and benefits against each other?" and (2) "What is most often the decisive factor in your decision as to whether the benefits outweigh the risks involved?"

Data Analysis

Open-ended questions with respect to the *identification and evaluation of risks and benefits* were organized into categories and reported as percentages (see Tables 3.3 through 3.5). The resulting categories were not mutually exclusive because IRB members could mention more than one risk or benefit (Table 3.3), methods for evaluating risks and benefits (Table 3.4) or decisive factor (Table 3.5).

Descriptive statistics were generated for the closed-ended questions with respect to *the estimation of risks and benefits*. The X^2 statistic was used to test the relationship between professional status and length of IRB membership, on the one hand, and the risk/benefit estimation on the other. Specifically, we compared the closed-ended responses of: (1) physicians (n=26) versus other professionals (n=27), (2) oncologists (n=9) versus other IRB members (n=44), and (3) those with 1-4 years experience as a member of an IRB (n=30) versus those with more than 4 years experience (n=23) with respect to: (a) the perceived adequacy of information typically available in phase II cancer protocols; and (b) the perceived competence to evaluate the scientific and risk/benefit ratio issues of those protocols. Results

pertaining to the identification and evaluation of risks and benefits were not submitted to subgroup analyses because the large number of categories derived from these qualitative data did not lend themselves to such comparisons. With respect to the identification of benefits to future patients and medical science, however, all respondents answered identical.

3.3 Results

Identification of risks and benefits

Not surprisingly, several different approaches to identifying the risks and benefits to patients were reported, ranging from critical reading of protocols and/or patient information to using one's own experience or consulting with experts and study coordinators for advice. Some IRB members reported focusing on the risks alone or on risks in relation to benefits, while others also consider the alternative treatment options for the patient group within and outside of the clinical trial protocol.

Table 3.3 displays the types of risks and benefits to patients participating in phase II clinical trials identified by IRB members. All of the respondents identified the toxicity and side-effects of treatment, and nearly all the additional burden associated with trial participation (e.g., frequent visits to the hospital, extra tests) as common risks associated with trial participation. Less self-evident was that 65% of the respondents identified psychosocial risks associated with trial participation. These included uncertainty about what is going to happen, a potential (and false) sense of hope about treatment efficacy, and confrontation with the fact that the disease cannot be cured; that the treatment may be of only limited or no direct benefit. Additionally, 20% of the respondents reported a decrease in quality of life as a risk of treatment.

Conversely, 68% of the respondents indicated a number of specific psychological benefits associated with participation in a phase II trial. These included an increase in the amount of attention and support received from medical and ancillary health care providers, a sense that there is still something that can be done to actively treat the disease, as well as a personal feeling of being able to "fight back" against the disease. Approximately one-third of the respondents identified improved quality of life as a potential benefit of trial participation. Approximately one-quarter of the IRB members interviewed identified treatment efficacy as a possible benefit. As expected, all respondents identified the potential for developing more effective cancer therapies as the primary benefit to future patients and to the scientific community.

Table 3.3: *Risks and benefits to phase II trial patients identified by IRB members (N=53)*

Type of risk	
Epected or unexpected side-effects and toxicity	100%
(Frequency of) visits to and stays in hospital and extra tests	96%

Psychological and social risks	65%
Decrease in quality of life	20%
Various other factors	17%
Type of benefit	
Possible treatment effect	24%
Increase in quality of life	37%
Psychological benefits	68%
Various other factors	5%

N.B. Percentages do not sum to 100% because respondents could mention more than one specific risk or benefit.

Estimation of risks and benefits

Perceived adequacy of information provided in protocols

As indicated in Table 3.1, only a small minority of the respondents (8%) indicated that phase II protocols typically contain too little information about the types of benefits that might accrue to participating patients. However, between approximately one-quarter and one-half of the respondents reported that there is frequently insufficient information provided about the likelihood, the magnitude and the duration of such benefits.

Similarly, most IRB members believed that protocols provide sufficient information about the types of risks involved in phase II clinical trials. However, a substantial percentage of the respondents indicated that too little information is available regarding the likelihood, seriousness, duration and reversibility of those risks (44%, 36%, 60% and 36%, respectively). Approximately 90% of the respondents indicated that sufficient information is provided regarding the potential importance of the clinical trial for future patients and for medical science.

Perceived competence in protocol evaluation

Between 15% and 34% of the IRB members reported that it was (very) difficult to judge the various risks and benefits associated with phase II clinical trials, both for participating patients and for future patients and society at large. While nearly all of the respondents indicated that they understood the aims (92%) and scientific relevance (94%) of phase II clinical trials, a substantial minority felt less than fully competent in evaluating the originality of the research (40%), the feasibility of the trial (34%), the scientific methodology employed (30%), the way in which the trial data were to be analyzed (42%), and how the trial relates to previous studies (32%).

Evaluation of risks and benefits

Table 3.4 shows the different ways in which IRB members go about evaluating the risks and benefits of phase II studies. Most of the decision strategies followed do not reflect a process of weighing risks and benefits against each other in a systematic way, but rather involve gaining an overall impression (20%), considering what alternative treatments are available (15%), or considering whether one would be willing to undergo the trial-based treatment oneself or would advise a family member to do so (10%). Seventeen percent of the respondents indicated that they typically leave the decision as to whether the benefits of a trial outweigh the risks to the patients themselves, and 12% reported that it is a task for the IRB as a whole, rather than for himself or herself as an individual IRB member.

Table 3.4: *Methods used to evaluate risks and benefits of phase II protocols (N=53)*

Weighing risks and benefits systematically	12%
Global estimation based on impressions or feelings	20%
Considering other treatment alternatives	15%
Considering whether one would participate oneself and/or advise a family member to do so	10%
Leave the evaluation to the patient	17%
Leave the evaluation to the IRB as a whole	
Overall judgement of IRB as a whole	12%
Various other methods	14%

N.B. The figures do not sum to 100% because respondents could mention more than one factor

The factors considered by IRB members to be decisive in assessing the risk/benefit ratio in phase II clinical trials are displayed in Table 3.5. Interestingly, one-third of the respondents were unable to identify such a factor in that they do not typically make such assessments themselves. The issue reported most frequently as being decisive was the potential value of the trial to future patients and to medical science (i.e., the potential of finding a more efficacious treatment) (21%). This was followed by the risks, burdens and inconvenience to participating patients (18%), the expectation that the

treatment would be beneficial to the participating patients (16%), and feeling comfortable in proposing the trial-based treatment to patients (11%).

Table 3.5: *Decisive factors in the assessment of the risk/benefit ratio of phase II protocols (N=53)*

Benefit to medical science	21%
The risks, burden and inconvenience to patients	18%
Reasonable expectation of benefit to the patient	16%
Feeling comfortable proposing trial-based treatment to patients?	11%
Would participate self or advise a family member to do so?	5%
Overall judgement of IRB as a whole	7%
Various other factors	14%
I do not make a risk/benefit calculation	34%

N.B. The figures do not sum to 100% because respondents could mention more than one factor

Professional status, length of IRB membership and RBR assessment

All respondents, regardless of professional background, identified the potential for developing better cancer therapies, with the resulting benefits to future patients and to medical science as possible benefits of phase II trials. Physicians and 'other professionals' also did not differ significantly with respect to the perceived adequacy of information contained in phase II trial protocols. However, a significantly greater percentage of the IRB members who were physicians reported feeling competent in assessing the originality of the research (58% versus 22%, $p < 0.05$), the methodology employed (62% versus 41%, $p < 0.01$), and whether the trial would yield new insights (77% versus 37%, $p < 0.05$) (data not shown in tabular form).

When comparing oncology specialists (i.e., medical, radiation or surgical oncologists) with other IRB members (including family physicians), statistically significant differences were observed in: (1) the perceived adequacy of information provided in trial protocols about the likelihood of benefits (100% versus 68%, $p < 0.05$) and risks (89% versus 49%, $p < 0.01$) to patients, and (2) perceived competence in evaluating the toxicity of the treatment (100% vs. 50%, $p < 0.05$), the invasiveness of the treatment (100% versus 55%, $p < 0.01$), the originality of the trial (89% versus 30%, $p < 0.05$), and the place of the trial in relation to previous research (89% versus 34%, $p < 0.05$) (data not shown in tabular form).

Relatively new IRB members (i.e., those who had been members for 4 years or less) were more likely than members of longer standing to report that trial protocols contain insufficient information on the likelihood of benefits (40% vs. 9%; $p < 0.05$) and the type of risks (23% vs. 14%, $p < 0.05$) to patients. No statistically significant association was found between length of IRB membership and perceived competence to evaluate trial protocols (data not shown in tabular form).

3.4 Discussion

The current study was undertaken to gain a greater understanding of a number of interrelated issues involved in the evaluation of the risks and benefits of phase II cancer trials by individual members of IRBs. First, we were interested in identifying the range of factors that IRB members take into consideration when evaluating the risk/benefit of such trials. Not unexpectedly, the toxicity and side-effects of treatment were most often cited as risks associated with participating in a phase II trial. However, psychological and quality-of-life factors were also very frequently identified as both potential risks and benefits of trial participation. These findings are in line with those of previous surveys of IRB chairmen and clinical trial principal investigators (Kodish et al., 1992), and suggest an intriguing asymmetry between the potential benefits of trial participation as cited by IRB members and those identified by trial patients. That is, previous studies have found that patients enrolled in cancer clinical trials overwhelmingly cite hope of physical, rather than psychological benefit as the primary motivation for their participation (Daugherty et al., 1995; Schaeffer et al., 1996; Miller, 2000). Additionally, our findings suggest that IRB members generally find it acceptable that patients undergo considerable physical risks in exchange for primarily psychological and quality-of-life benefits for themselves, as well as potential clinical benefits for future patients and medical science.

Second, we investigated the perceived adequacy of the information typically available in phase II protocols, and the perceived competence of IRB members to make risk/benefit assessments. Although the large majority of IRB members indicated that trial protocols contain sufficient information about the types of risks and benefits involved in phase II trials in general, a substantial percentage (between approximately 25% and 60%) reported that too little information is available about more specific issues such as the likelihood, magnitude, and duration of such risks and benefits. This does not necessarily mean that phase II clinical trial protocols are poorly written. In some cases, it may not be possible to estimate accurately the exact nature of the risks and benefits involved. Nevertheless, the lack of detail provided in protocols may explain, at least in part, the finding that approximately one-third of IRB members do not make a risk-benefit calculation at all, and that 17% leave such matters up to the patients. This latter finding is somewhat disconcerting in light of the evidence that patients are often unable to fully understand the information provided to them about the clinical trials in which they are invited to participate (Daugherty et al., 1995; Schaeffer et al, 1996; Aaronson et al, 1996).

A substantial minority of IRB members (ranging from 15% to 40%) reported feeling less than fully competent to evaluate the risks and benefits associated with phase II trials and the scientific details of phase II trial protocols. While these findings may give cause for concern, they need to be tempered by the fact that protocol evaluation is typically a multidisciplinary, group process. It may not be realistic or necessarily efficient to expect that every individual member of an IRB is capable of evaluating all aspects of a clinical trial. Additionally, although not typically the case in the Netherlands, some hospitals have separate committees for

evaluating the scientific versus ethical/human subject protection aspects of clinical trial protocols.

Third, we inquired into the methods employed by IRB members to arrive at a risk/benefit estimate, and the most important factors taken into consideration in such estimates. Only a small minority of the respondents indicated that they weighed risks and benefits against one another in a systematic way. More typically, such evaluations are made at a more global level, based on both individual judgments regarding the acceptability of the trial, whether one would participate oneself, and on the results of the decision-making process of the IRB as a whole. It is unclear as to whether a more formal and systematic form of individual risk-benefit evaluation would yield different decisions. It might, however, foster greater clarity in the criteria used to reach decisions, and greater consistency in the application of such criteria across IRBs.

Finally, we investigated whether there are systematic differences in risk-benefit assessment as a function of the professional background and number of years of committee experience of IRB members. As might be expected, physicians (particularly those specialized in oncology) and IRB members of longer standing were less likely than other IRB members to report inadequacies in the information provided by phase II trial protocols, and indicated having less difficulty in evaluating the various scientific aspects of those protocols. Similar results have been reported in studies of IRBs, in general (i.e., not specifically focused on cancer clinical trials) (Berghmans et al., 1996, 1997).

The current results need to be interpreted in the light of certain study limitations. First, we did not distinguish between different types of phase II protocols (e.g., chemotherapy, radiotherapy or surgery). While we have no reason to believe that this would have a significant impact on the findings, it is something that merits further study.

Second, as noted above, the focus of our research was on the individual members of IRBs. The decisions made by IRBs, and the discussions that form the basis of such decisions, are of a collective nature. Each IRB member contributes to the decision-making process from his or her professional perspective and, undoubtedly, the whole is more than the sum of its parts. Thus, a more dynamic, group-oriented research approach is needed to obtain a comprehensive picture of both the process and content of risk-benefit assessment. Hopefully, the fourth phase of our investigation, in which we observed and analyzed the meetings of several IRBs, will shed additional light on the decision-making process, and the role of individual members in that process.

Third, our study was restricted to members of IRBs from Dutch academic hospitals and specialized cancer treatment centers. IRBs in various European countries and in North America may differ in some respects (e.g., with regard to informed consent requirements, the need for hospitals and physicians to protect themselves against potential legal risks, etc.). Nevertheless, the basic structure, objectives and procedures for protocol review are quite similar across countries, and thus we believe that our results can reasonably be extended to other national systems of research oversight. Nevertheless, this needs to be confirmed empirically.

In summary, the results of this study indicate that there is a good deal of variability in the ways in which *individual* members of IRBs identify, estimate and evaluate the risks and benefits associated with phase II clinical trials in oncology. A substantial minority of IRB members believes that trial protocols provide too little information relevant to evaluating various cost/benefit and scientific issues, and feels less than fully competent in carrying out such evaluations. In general, IRB members are more likely to identify psychosocial benefits than physical health benefits that may accrue to patients participating in phase II trials. They view such trials primarily as a vehicle for testing new therapies that may be of benefit to future patients and to medical science, in general. While this is in line with the goals and objectives of the vast majority of phase II trials, it may not reflect the expectations of patients themselves, who often choose to participate in such trials in the hope that the treatment will prove to be clinically effective. This underscores the need to provide potential phase II clinical trial patients with sufficient information to make informed decisions, and to ensure that such decisions are appropriately motivated.

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*4 The evaluation of phase II and III cancer clinical trials by Institutional Review Board (IRB) members **

Summary

Background: This study examined the opinions of Institutional Review Board (IRB) members about the assessment of the risk-benefit ratio (RBR) of phase II and III cancer clinical trials.
Methods: Semi-structured interviews were conducted with 53 members of IRBs from 4 academic hospitals and 2 specialized cancer centers in the Netherlands.
Results: Lack of evaluation criteria, uncertainty concerning the benefits to patients, and insufficient information about the study rationale were mentioned most frequently as difficult aspects in RBR assessments of phase II and III cancer protocols. Fifty-six percent of the IRB members indicated that they could benefit from additional information and education in making risk-benefit assessments of such protocols. A similar percentage believed that more insight into the experiences of the patients involved in such trials, and their perceptions of the associated risks and benefits, could be useful to them in making RBR assessments. Forty-eight percent of the IRB members supported the inclusion of lay individuals in IRBs, but only 23% believed that it would be appropriate to include patients.
Conclusions: More than half of the IRB members expressed interest in obtaining more information and education in making RBR assessments for phase II and III cancer protocols. Many also believed that better insight into the patients' perspective could aid them in making such assessments. However, only a minority of IRB members would favor including patients on IRBs.

4.1 Introduction

The Declaration of Helsinki and other national and international regulations oblige Institutional Review Boards (IRBs) to weigh the risks of medical research against its benefits, and to assess the ratio between the two. In order for a study to be approved, this risk-benefit ratio (RBR) must be "favorable," "in balance," or "proportional" in the IRB's opinion. IRBs have the responsibility of protecting research participants against studies that carry with them too many risks. This assumes that IRBs are sufficiently aware of which risks the medical research community and society, in general, find acceptable in relation to which benefits. The extent to which this assumption is justified in practice is open to question, especially considering the vague description of this requirement in the

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various regulations. The requirement further presupposes that IRBs (and IRB members) know what trial participants find important with respect to their protection. Whether this assumption is justified is also unknown.

The absence of clear criteria has been identified as a weak link in the IRB evaluation process (Meslin, 1993a,b). Previous studies have indicated that
IRB members find RBR assessments to be one of the most difficult tasks involved in reviewing protocols (Berghmans et al., 1996; Goldman & Katz, 1982; Levine & Katz, 1984; Gilbert et al., 1989; Miller, 1989; Meslin, 1990; Hall, 1991; Meslin, 1993a,b; Bjune & Gedde-Dahl, 1993; Harries et al., 1994; Foster et al., 1995; Berghmans et al., 1996; While, 1996). Little is known, however, about the kinds of difficulties IRB members experience when making RBR assessments, and whether the members need assistance in making these assessments. Whether IRB members find it desirable to have lay individuals and patients participating in IRBs with respect to RBR assessments is also unknown. In a previous study, we found that a substantial minority of IRB members believed that phase II cancer clinical trial protocols provide too little information relating to the evaluation of various cost-benefit and scientific issues, and felt less than fully competent in carrying out such evaluations (Van Luijn, 2000; Van Luijn et al. 2002). The study also revealed that only a small minority of IRB members weigh risks and benefits against one another in a systematic way, rather than intuitively. More typically, risk-benefit evaluations are made on a more global level, based on both individual judgments regarding the acceptability of the trial, and on the results of the IRB decision-making process as a whole. Finally, approximately one-third of IRB members did not determine the RBR ratio themselves, but rather preferred to leave that to the individual patients.

In the current paper, we report on a study that sought to determine which aspects of the RBR assessment of phase II and phase III cancer clinical trials individual IRB members find the most difficult, whether they require more information and education in making such assessments, how the process can be improved, and whether the participation of lay individuals and patients is viewed as a means of improving the quality of the assessments.[3]

[3] Phase II and III cancer clinical trials both study questions of therapeutic effect. Phase II trials, typically involving a limited number of patients, and addresses the question of whether a new therapeutic agent or treatment has an anti-tumor effect. Phase III clinical trials are typically larger in size, and randomize patients between a standard and an experimental treatment.

4.2 Patients and methods

Study subjects

Members of the IRBs of six hospitals in the Netherlands were invited to participate in the study, including the academic hospitals of the universities of Utrecht, Rotterdam, and Leiden, the Vrije Universiteit in Amsterdam, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in Amsterdam, and the Daniel den Hoed Cancer Center in Rotterdam. Sixty-five IRB members were approached, of whom 53 (81%) agreed to participate. The remaining twelve individuals declined to participate due to the time-consuming nature of the research. The participating IRB members included medical specialists (41%), family physicians (8%), nurses (15%), and other disciplines (36%), including four pharmacists, two ethicists, two social scientists, one statistician, and one attorney, among others. The age of the participants ranged from 28 to 69 years. The majority (64%) was male. Nine percent had served on the IRB for less than one year, 47% for between one and four years, and 44% for four years or longer.

Study measures: the semi-structured interview

Semi-structured interviews, including a combination of open- and closed-ended questions, focused on the most difficult aspects in assessing the RBR of phase II and phase III cancer clinical trial protocols, the perceived need for additional information and education in making RBR assessments, suggestions for improving these assessments, and the desirability of having lay individuals and patients participate in IRBs. On average, the interview took approximately one hour to complete.

Risk-benefit assessments of phase II and III cancer protocols

The interviews included two open-ended questions concerning the most difficult aspects of assessing the risks and benefits of phase II and phase III cancer protocols. One closed-ended question concerned the difference between RBR assessments of phase II and III cancer trials and other medical research: "Is it easier or more difficult for you to evaluate phase II and III cancer protocols than it is to evaluate other protocols on risk-benefit and scientific issues, or do you see no difference?"

Need for more information and education in the RBR assessment process and suggestions for improving these assessments

The interviews included three open-ended questions concerning the need for more information and education, and suggestions for improving the risk-benefit assessment process for phase II and III cancer protocols:

1. **"Do you need more information and education in assessing the RBR of protocols?"**
2. **"What kind of information and education do you need?"**
3. **"Do you have any suggestions that would make the RBR assessment process easier for you?"**

Desirability of having lay individuals and patients participate in IRBs

"Two closed-ended questions concerned the desirability of having lay individuals and patients participate in IRBs:

1. "Do you believe that it is desirable for lay individuals (other than patients) to participate in an IRB?"
2. "Do you believe that it is desirable for patients (e.g., potential trial participants) to participate in an IRB?"

Responses were scored on a 4-point Likert scale from 1 (very desirable) to 4 (not desirable at all). Respondents were asked to describe the reasons underlying the responses that they provided to these questions.

Data analysis

Open-ended questions concerning the most difficult aspects of assessing the RBR for phase II and III cancer protocols, the type of support needed to make RBR assessments, and suggestions for improving these assessments were organized into categories and are reported as percentages. The resulting categories were not mutually exclusive, as respondents could mention more than one difficult aspect of RBR assessment (Table 4.1), type of support needed (Table 4.2), or suggestion for improving RBR assessments (Table 4.3). Responses are illustrated in the text with salient statements made by IRB members.

Descriptive statistics were calculated for responses to the closed-ended questions concerning the risk-benefit assessment of oncology protocols (as compared to other protocols) and the desirability of having lay individuals and patients participate in IRBs. Chi-square statistics were used to test whether the background characteristics of the IRB members (e.g., age, gender, professional background, years of experience on IRBs) were associated significantly with perceived need for information and training, and attitudes towards lay and patient membership on an IRB.

4.3 Results

Assessing the risk-benefit ratio of phase II and III cancer clinical trials

As reported in Table 4.1, making RBR decisions without clear criteria and in the face of uncertainty with regard to patient benefits and study rationale were perceived as the two most difficult aspects of the RBR assessment process for phase II and III cancer trials. Specific issues mentioned by respondents during the interview included the difficulty in comparing risks with benefits, inadequate knowledge of the acceptability of certain risks, and an inability to imagine the impact of a failed clinical trial-based treatment on patients' lives. Some respondents reported that they try to imagine whether they would want to participate themselves, but found this to be difficult. Still others indicated that they, while they often would not want to participate themselves or advise

Table 4.1: *Opinions of IRB members concerning the most difficult aspects of assessing the RBRs of Phase II and Phase III cancer trials (N=53)*

	Phase II	*Phase III*
Lack of criteria to assess the RBR	62%	39%
Uncertainty about the benefits to patients and the study rationale	41%	37%
Doing research/confronting patients with difficult choices in the face of necessary risks	15%	0%
Gaining a view of all relevant factors	12%	2%
Withholding treatment because of placebo	0%	10%
Various other aspects	21%[a]	27%[b]

[a] e.g. No feedback on study results, therefore it remains unclear whether the estimation and evaluation of risks and benefits was correct; communication with other IRB members about the RBR; the researchers' reaction if the protocol is rejected.

[b] e.g. No feedback on study results; uncertainty about toxicity; the perhaps unrealistic hope that is provided to patients by letting them participate in the study.

N.B. The percentages do not total 100% because more than one response could be given.

their loved ones to do so, this was not something that they could easily factor into their RBR assessment. Statements made by several of the respondents illustrated nicely some of the major difficulties experienced by IRB members in evaluating the RBR of trials:

> "The most difficult part is that you cannot really imagine the patient's position. How does it feel to have cancer? You cannot know that unless you have cancer yourself. Your standards for quality of life change at that point. I often hear IRB members say, 'I would never take part in this study myself, but the patients really want to participate" (Statistician).

> "The problem is that there are major uncertainties about the chance of risks and the chance of benefits, and that you are expected to compare apples with oranges. Risks and benefits are not given in comparable parameters. How do you weigh pain and hair loss against living a few months longer?" (Surgeon).

> "The most difficult aspect is imagining what a patient will go through in such a study. I know that, in general, the benefits of Phase II studies are minimal for both the participants and for medical science. They're just selling hope" (Family physician).

Sixty percent of the IRB members from the 4 academic hospitals (where clinical trials from a wide range of medical fields are reviewed), reported experiencing no differences in evaluating the RBR of oncology versus other types of protocols, 38% reported more difficulty in evaluating cancer protocols, and 2% found other types of protocols more difficult to evaluate.

Need for more information and education in assessing the risk-benefit ratio of phase II and III cancer clinical trial protocols

Fifty-six percent of the IRB members reported that they would like to receive more information about and education in assessing the RBR of protocols. As indicated in Table 4.2, approximately half of those respondents who expressed interest in receiving more information or training favored courses or seminars, and one-third indicated a desire to obtain feedback on trial results and on the experiences of patients who participate in trials. Several direct quotes serve to illustrate this:

> "More guidance would be useful. You can learn a lot from feedback concerning the results of phase II and III studies. It is important that the IRB be provided with a feedback system" (Pharmacologist).

> "To ask a large group of patients how they have experienced the trial and how they look back upon their participation. I think this will be very important to me with respect to the evaluation of protocols" (Nurse).

The remaining 44% of the IRB members expressed no additional need for assistance in the RBR assessment of protocols, as they felt that the IRB meetings themselves provided sufficient training opportunities and sources of information.

Table 4.2: *Type of information and education desired by IRB members in assessing the RBR of phase II and III cancer clinical trials (N=30)* [a]

Courses or seminars	52%
Feedback on patients' trial experiences and trial results	32%
Reflection on past decisions/overview of new developments in oncological research	8%
Various [b]	36%

[a] *Only IRB members who said that they needed more knowledge and education answered this question.*

[b] Including: RBR assessment by researchers; methodological aspects; how to apply general ethical concepts to particular protocols; guidelines about how to assess the RBR; feedback on individual IRB performance; more training in legal matters and animal research; a list with important things to think about for every member.

N.B. The percentages do not total 100% because more than one response could be provided.

Suggestions for improving RBR assessment of Phase II and III cancer protocols

As shown in Table 4.3, more than half of the IRB members reported wanting more information, particularly relating to the experiences of patients with clinical trials and their perceptions of the risks and benefits involved. As one family physician put it:

> *"It is very important to know how patients experience trials. A lot is taken for granted. Oncologists often believe that patients always are searching for hope. It is debatable, however, whether this is true. In general, IRBs assume that patients want hope and thus choose to be treated. I would like other IRB members to receive more training with regard to what patients experience, and I would like to know more about the medical and oncological aspects."*

Approximately one quarter of the respondents reported that it would be helpful if investigators themselves were to include their own RBR assessments as part of the trial protocol. Additional training and the use of a checklist in order to review all of the major issues involved in RBR assessments were also mentioned as possibly helpful in facilitating the review process. Other suggestions included providing more feedback on trial results, ensuring that a broader range of disciplines representing the patients' perspective is represented on IRBs, having access to a database containing the results of earlier studies, and encouraging more critical discussions between IRB representatives and researchers prior to or during IRB-meetings.

Table 4.3: IRB members' suggestions for improving the risk-benefit assessment of Phase II and III cancer clinical trials (N=53) [a]

More knowledge available on trial experience/ risk-benefit perceptions of patients	56%
RBR assessments by researchers	26%
Additional training and checklists for IRB members	23%
More time for preparation and discussion/ contact with researchers	9%
Improvement of IRB discussions	7%
Various	28%

[a] *The percentages do not total 100% because more than one suggestion could be given.*

Membership of lay individuals and patients in the IRB

Forty-eight percent of IRB members were in favor of having lay members serve on IRBs (Table 4.4). They believe that lay individuals can offer fresh perspectives, are focused more on the psychosocial consequences of trial-participation, and can form a counterweight to the other members who are typically involved themselves in doing research.

Of the remaining respondents, 44% were opposed to having lay individuals as IRB members, and 8% had no opinion on the matter. The primary reasons for opposing lay members were: (1) a belief that lay individuals would not make any substantial contribution; (2) concern that the task would be too difficult for lay individuals; and
(3) a belief that the lay perspective was already sufficiently represented (e.g., via nurses).

The majority of respondents (54%) opposed the idea of having patients *participate on the IRB. Those who rejected this proposal did not believe that patients had any specific contribution to make, were concerned that open discussions would be hampered, believed patients would make judgments solely on the basis of their own, personal experiences, or felt that participation on an IRB would simply be too difficult or would impose too great a burden on patients. Still others believed that the logistics would be difficult because different patients would be needed for different protocols, or that it would be difficult to find a single patient who could represent the diverse population(s) of patients.*

Twenty-three percent of the IRB members considered it desirable to have patients on IRBs, and the remaining 23% expressed no opinion. Most of those favoring patient participation considered patients to be "experiential experts" who could inform other IRB members about the meaning of risks and benefits. Others believed that patients are better able to evaluate the quality of written patient information than other IRB members.

Table 4.4: *IRB members' opinions about the desirability of having lay individuals and patients participate in IRBs (N=53)*

Lay participation on IRBs is desirable	48%	
Lay participation on IRBs is not desirable		***44%***
Don't know/no opinion	8%	
Patient participation on IRBs is desirable	23%	
Patient participation on IRBs is not desirable	54%	
Don't know/no opinion	23%	

The effect of IRB members' background characteristics

Physicians did not differ significantly from other professionals in their opinions about the need for more information and education in making risk-benefit assessments of phase II and III cancer protocols. This was also the case for nurses compared to other professionals. However, significantly fewer oncologists believed that they could benefit from more information and education than did other professionals (18% versus 62%; $p < .05$). No statistically significant associations were found between duration of IRB membership, age or gender and the perceived need for more information and education.

A significantly larger percentage of younger IRB members (age < 40) favored lay participation in IRBs than did older members (70% versus 38%; p =. 05). No other background variables were related significantly to opinions regarding lay membership.

Relatively new IRB members (those with four or fewer years of experience) were significantly more likely to favor patient participation on IRBs than were members with more experience (38% versus 4%; p=.02). Although not statistically significant, fewer physicians than other professionals favored having patients as members of IRBs (12% versus 35%).Finally, female IRB members rejected the idea of patient IRB participation significantly more often than did their male counterparts (72% versus 44%; p = .02).

4.4 Discussion

The objective of this study was to provide greater insight into the RBR assessment process for phase II and III cancer clinical trials as experienced by individual members of IRBs. We first sought to identify the most difficult aspects of the RBR assessment of phase II and III protocols. The lack of RBR assessment criteria, and uncertainty concerning the benefits to patients and the study rationale were reported as the most difficult aspects of the process. Other studies have also found a lack of clear criteria for evaluating the RBR assessment and board members' lack of technical expertise necessary for weighing the risks and benefits against each other to be major problems (Meslin, 1989; Meslin et al. 1994; Churchill et al. 2003).

In our previous study we found that one-third of IRB members could not report a decisive factor in their assessment of the RBR of Phase II cancer protocols, because they did not determine this ratio themselves, but left it to the patients (Van Luijn, 2000; Van Luijn et al., 2002). It is not unthinkable that lack of decision-making criteria and uncertainty concerning both the benefits to patients and the study rationale, could explain why many IRB members apparently prefer not to evaluate the RBR of such protocols.

We were also interested in determining whether Phase II and III cancer trials were considered more difficult to evaluate than were other medical research protocols. The majority of IRB members experienced no differences in this regard. This suggests that our findings on the RBR assessments of cancer protocols may

also apply to the evaluation of medical research, in general. This is, of course, something that would need to be confirmed empirically.

Second, we investigated the needs expressed by IRB members for more information and education in assessing the RBR of phase II and III cancer protocols and their suggestions for improving their assessments. Almost two-thirds of the respondents reported that additional information and education would be welcome. Most expressed a desire to attend courses or seminars or to receive feedback concerning the trial experiences of patients, as well as results from the trials. Although courses are available for IRB members in the Netherlands, they are not mandatory and only a small percentage of members attend them.

The IRB members made a number of suggestions regarding possible ways to improve RBR assessments of phase II and III cancer protocols. Most indicated that they would like to receive more information about patients' trial experiences and risk-benefit perceptions. In addition, the availability of RBR assessments made by researchers themselves, checklists for IRB members, and more training facilities were mentioned as ways of improving RBR assessments. In particular, these findings indicate that knowledge is currently lacking concerning the perceptions and experiences of patients. In addition, the findings suggest a striking tension in IRB members' apparent lack of insight into the patient perspective (i.e. the *meaning* of the risks and benefits to patients) and their actual task (protecting human subjects against medical research that carries too many risks). Fifty-six percent of IRB members believed that more knowledge about patients' experiences with and perceptions of these issues could improve their RBR assessments. This also suggests that, to be capable of assessing the RBR (i.e. to have criteria for weighing risks and benefits against each other), more knowledge of the patients' perspective is needed.

To determine whether their decisions are ethically justifiable, IRB members must imagine the consequences of their decisions for patients (Martin et al., 1995). It is impossible, however, to know how others will actually assess these consequences; an IRB member can make only a rough guess of what their decisions will mean to others (Martin et al. 1995). Risk-benefit assessments depend on the relative importance of the different factors to be weighed. More insight is needed, therefore, into the *values and goals* of patients, if IRBs are to be capable of determining their importance, and if risk-benefit criteria are to be well chosen (Ackerman, 1995).

Third, we asked IRB members their opinions about the desirability of having lay individuals and patients participate in IRBs. Lay members are relatively common in IRBs in the U.S. and in some European countries (also in several IRBs in the Netherlands), Results of a Danish study indicated that lay members are capable of signaling inadequate risk-benefit assessments and often made the most useful comments about ambiguities in the consent forms (Holm, 1992). Others have emphasized the importance of lay individuals' uniquely informed estimations of the severity and importance of risks and benefits for IRB review (Reinders, unpublished paper). Experiences with patients reviewing AIDS protocols have been positive (Till et al., 1992), and patients estimate the severity of certain risks in a manner that differs considerably from that of physicians and nurses (Slevin et al. 1990). Nevertheless, although the respondents in the current study indicated that more

insight into the patients' perspective could facilitate their making RBR assessments, less than half were in favor of having lay members of IRBs.

Finally, we studied the effect of background characteristics on IRB members' ratings. Not surprisingly, we found that fewer oncologists felt the need for more information and education in making RBR assessments than did other professionals. Female IRB members and those who had been involved in IRBs for a longer period of time tended to be less favorable toward having patients participate in IRBs. Also, older members tended to be less supportive of having lay individuals on IRBs. It may be that older members and members with a longer association with an IRB believe that their experience provides them with sufficient insight into the protocol review process, or they may simply have more conservative views about who should be represented in IRBs. Why fewer female IRB members are in favor of having patients participate is unclear. Although most nurses in this study were female, there were also many females from other professions, and being a nurse had no significant relationship with attitudes towards patient participation.

The current results must be interpreted in light of certain limitations of the study. First, the study did not distinguish among the various types of phase II and III protocols (e.g. chemotherapy, radiotherapy, or surgery). While there is no reason to believe that this would have a significant impact on the findings, the issue does merit further study. In addition, respondents were not asked to distinguish between protocols arising from within their own institutions and those from other sources (either national or international). Attempts to obtain systematic data on this matter from the participating IRBs proved unsuccessful, because such information is not routinely registered in databases and is thus not readily accessible. Additional research is needed, therefore, to determine whether the perceptions of difficulties associated with assessing the RBR of protocols and the need for information and education vary significantly according to their source (e.g. local versus national or international; academic versus industry).

As a second cautionary note, the focus of our research was on the individual members of IRBs. The decisions made by IRBs as a whole, and the discussions that form the basis of such decisions, are of a collective nature. Each IRB member contributes to the decision-making process from a unique professional perspective, and the whole is undoubtedly more than the sum of its parts. A more dynamic, group-oriented research approach is also needed, therefore, to obtain a comprehensive picture of the issues surrounding risk-benefit assessments.

In summary, part of the results of this study indicate an intriguing paradox. On the one hand, a lack of criteria and uncertainty about the benefits to patients and the rationale of the study make RBR assessments of phase II and III cancer trials difficult, most IRB members would like to receive additional information and education in assessing the RBR of such trials, and most believe that additional insight into the experiences and perceptions of patients would help improve the assessment process. On the other hand, for about half of the Dutch IRB members, having patients participate on IRBs appeared to be an unworkable solution to this lack of familiarity with the patients' perspective. We therefore conclude that –

beyond the availability of RBR assessments made by researchers themselves, checklists for IRB members, and more training facilities (also often mentioned suggestions by IRB members for improvements of RBR assessments) - more empirical research is needed into the trial experiences and perceptions of patients. There are some indications that patients' experiences of recruitment to early cancer trials and their perceptions of the informed consent process, reflect a lack of understanding of what they were taking part in, and that the psychological, emotional and social impact of taking part in clinical trials is better uncovered by in-depth interviews than by standardized quality of life questionnaires (Daugherty, 1999; Joffe et al, 2001; Cox, 2002; Cox, 2003). Additionally, studies are needed to investigate the effects, both positive and negative, of having lay individuals or patients participating in IRBs. Both lines of research would be promising first steps toward improving the RBR assessments of Phase II and III cancer clinical trials by IRB members.

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5 The evaluation of the risks and benefits of phase II cancer clinical trials by Institutional Review Boards (IRB) members: A case study *

Summary

Objectives: There are indications that IRB members do not find it easy to assess the ratio of the risks to the benefits in medical experiments, although this is a principal duty of Institutional Review Boards (IRBs). This study examined how Institutional Review Board (IRB) members assessed the risk/benefit ratio of a specific Phase II breast cancer clinical trial.

Subjects and methods: The Phase II breast cancer clinical trial was evaluated by means of a questionnaire administered to 43 members from IRBs at six research hospitals and specialized cancer centers in the Netherlands. The following topics were addressed in the questionnaire: (1) the identification and estimation of the inconvenience, toxicity, psychosocial distress, and the benefits of trial participation to patients, (2) the identification and estimation of benefits to future patients and medical science, (3) the evaluation of the importance of specific risks and benefits in the risk/benefit ratio of the trial, (4) the assessment of the risk/benefit ratio of the study, and (5) the assessment of the ethical acceptability of the study.

Results: (1) Most IRB members expected trial participation to carry with it fairly or very serious inconveniences, fairly severe to sometimes life-threatening toxicity, and serious psychological and social consequences. Conversely, the perceived likelihood of benefits to patients was modest. (2) Most regarded the study to be important, the ratio between risks and benefits to be favorable, and believed that the protocol should be approved. Significant relationships were found between several specific risks and the overall RBR assessment. Of the benefits, the duration of tumor remission and symptom-free survival, and the perceived importance of tumor remission were related significantly to the assessment of the overall RBR and to the ethical acceptability of the trial. (3) There was a significant relationship between the assessment of the RBR and of the ethical acceptability of the trial. (4) If corrected for other IRB characteristics, only gender was significant with respect to the evaluation of the ethical acceptability of the trial.

Conclusions: (1) Most IRB members felt competent to estimate specific aspects of the risks and benefits such as likelihood and severity, to determine the RBR, and to assess the ethical acceptability of the trial. (2) Although IRB members state that they do attach a heavy weight to the risks, their final judgment on the trial's ethical acceptability is only significantly correlated to the benefits of the duration of remission and symptom free survival and not to the risks or the other studied benefits to participating patients.

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5.1 Introduction

There are indications that institutional review board (IRB) members do not find it easy to assess the ratio of the risks to the benefits in medical experiments, although this is one of their principal duties (Meslin, 1989; Meslin, 1993a,b; Berghmans et al., 1996, 1997). Not only do IRB members have difficulty identifying the relevant risks and benefits of a particular protocol, they also find it difficult to compare those risks and benefits because (1) the nature, extent and the duration of risks and benefits are often uncertain, (2) the nature of the various risks and benefits is very diverse, and (3) all of the risks accrue to the research subjects, while some of the benefits accrue to future patients and/or to medical science.

IRBs are legally required to evaluate whether the risk/benefit ratio (RBR) is 'reasonable', 'proportional' or 'favorable'. Since there is no consensus on the content of, and categories and criteria for evaluating the RBR, IRB evaluations, although usually based on long-term clinical experience, are unavoidably subjective and intuitive. The lack of shared categories and criteria makes it difficult to trace and discuss differences of opinion within an IRB, and thereby reduces the chances that the evaluation of the ratio between risks and benefits will play a prominent role in the final decision regarding the ethical acceptability of the research. The difficulties with assessing the RBR sometimes induce IRBs to leave the evaluation primarily to the potential research subjects, arguing that it is their right to determine whether, from their perspective, the relation of risks to benefits is reasonable. Whether this is ethically acceptable, and whether very ill patients are capable of making such stressful decisions, remains unclear (Schaeffer et al., 1996; Cox & Avis, 1996; Cheng et al., 2000; Montgomery et al., 1999; Huizinga et al., 1999; Davis et al., 1998).

The most important contributions to the study of RBR assessment of medical research involving humans have been those of Levine and Meslin (Meslin, 1989; Meslin, 1990, 1993a,b; Meslin et al., 1994; Levine, 1978; Levine, 1986; Martin et al., 1995). Levine (1986) developed a set of categories to distinguish between risks and benefits for participating patients, for future patients and for society at large (scientific progress). These categories have been further refined by distinguishing between different kinds or dimensions of risks and benefits for participating patients (e.g. physical, psychological, social). Meslin (1989) devoted special attention to risk assessment by IRB members. He identified three 'decision-making processes' in risk assessment: identification, estimation and evaluation of risks. Using Levine's and Meslin's distinction between different types of risks and benefits, between 'risk' and 'harm', certain and uncertain risks, and between the phases of identification, estimation and evaluation of risks, we designed a survey to assess IRB members' assessment of the RBR for a specific phase II cancer clinical trial.

The current study represents the second stage of a four-stage project examining the assessment of the RBR of phase II and III cancer clinical trials by IRB members in the Netherlands. The first stage of the study consisted of semi-structured interviews with 53 IRB members regarding the RBR assessment of phase II and III cancer clinical studies in general (Van Luijn, 2000; Van Luijn et al., 2002). This second stage of the research addresses three primary questions: (1) What risks and benefits do IRB members identify in a phase II breast cancer trial, and how do

they estimate and evaluate these risks and benefits? (2) What is their assessment of the risk/benefit ratio and the ethical acceptability of the protocol, and is there a relationship between the various risks and benefits and the assessment of the RBR, and the ethical acceptability of the trial? and (3) Are there systematic differences in assessment of the risk/benefit ratio and the ethical acceptability of the protocol as a function of IRB members' background characteristics?

5.2 Subjects and methods

Study subjects, protocol evaluation and questionnaire

The study was conducted in 1998–1999. The IRBs of 8 Dutch academic hospitals and specialized cancer centers were asked to participate in the study. We did not select non-academic hospitals because they do not evaluate sufficient numbers of cancer clinical trials to be appropriate candidates for such a study. Five of the 8 IRBs agreed to participate. All members of these IRBs (N=64) were invited to take part in the first stage of the study, of whom 52 agreed to do so. One IRB member of the IRB of a sixth Dutch teaching hospital also agreed to participate. The primary reason for not participating was constraints on time. Of these 53 IRB members, 10 declined to continue participation in this second stage of the research, again, due largely to time constraints. The final study sample on which the current analysis was based included 43 members of 6 IRBs in 6 Dutch hospitals.[4] The study sample consisted of oncologists (21%), other medical specialists (19%), family physicians (5%) nurses (19%) and other disciplines (36%), including four pharmacists, two ethicists, two behavioral scientists, one statistician, and others. Respondents' age ranged from 28 to 69 years. The majority was male (65%). Nine percent had been IRB members for less than 1 year, 47% for 1-4 years, 23% for 4-7 years, and 21% for longer than 7 years.

An American phase II breast cancer clinical trial –that had been approved in 1997– was selected for the study from the website of the National Cancer Institute.[5] We decided against a European or a Dutch protocol to avoid the chance of distortions in the results due to the possible familiarity of the research subjects with the protocol. This phase II trial was designed to investigate the efficacy and toxicity of allogeneic stem cell transplantation in combination with high doses of chemotherapy for patients with metastatic breast cancer. We selected a trial involving a very intensive treatment because we believed this to be the most effective approach to investigating the process of risk/benefit assessment. This trial differs from the usual phase II studies because it was expected to have high risks as well as potentially large benefits, while most phase II trials are expected to be less risky as well as less beneficial. The rationale for using this "atypical" trial was as follows. We expected that such a trial would result in more variation in IRB members' assessments of the risk/benefit ratio and of the ethical acceptability of the protocol than a study with high risks but small benefits or vice versa, or a study with low risks as well as small benefits. The protocol evaluation was conducted by means of a questionnaire consisting primarily of closed-ended questions. We used closed questions, because open questions about the protocol evaluation would

[4] The hospitals were the Utrecht Academic Hospital, the Vrije Universiteit Medical Center in Amsterdam, the Rotterdam Academic Hospital, the Leiden Academic Hospital, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in Amsterdam and the Daniel den Hoed Hospital in Rotterdam.

[5] The trial was used with permission of the authors and is entitled A Pilot study of Allogeneic Peripheral Blood Stem Cell Transplantation for Patients with Metastatic or Recurrent Breast Cancer Using a Conditioning Regimen of Busulfan and Cyclophosphamide.

be asked in in-depth interviews in the third phase of the research project. The questionnaire had been previously pilot-tested among 5 IRB members or former IRB members, none of whom participated in the main study. The respondents were asked to study the protocol and the patient information, to complete the questionnaire and to return it by mail. The procedures took approximately two hours: one hour for studying the protocol and 30 to 45 minutes to fill out the questionnaire.

The following topics were included in the questionnaire: (1) the identification and estimation of the inconvenience, toxicity, psychosocial distress, and the benefits of trial participation to patients, (2) the identification and estimation of benefits to future patients and medical science, (3) the evaluation of the relative importance of specific risks and benefits, (4) the assessment of the overall risk/benefit ratio of the study, and (5) the assessment of the ethical acceptability of the study. The questions that were asked were based on the literature and can be found in the Appendix (Meslin, 1989; Meslin, 1990, 1993a,b; Levine, 1978, 1986; Meslin et al., 1994, Martin et al., 1995). Although this protocol does not provide any data about psychological and social risks, we have asked whether IRB members believed these type of risks were present in the study. The questions concerning the identification and estimation of the toxicity were based on a predetermined list of toxicities drawn from the protocol itself. The specific aspects of possible treatment toxicity that were assessed included: likelihood, severity, duration, reversibility and amenability to treatment. The only aspects considered to be relevant for assessing the psychosocial burden of the treatment were likelihood, severity, and duration. The only aspects considered to be relevant for assessing the benefits of treatment were likelihood, duration and importance. The importance of the benefits of the treatment was assessed directly, while that of the risks was captured by the severity rating.

It might be argued that the details presented on the rating of the toxicity and benefits would be more relevant if a comparison were made with the actual 'facts' as stated in the protocol. However, in this study such a comparison was not of primary interest or the focus of research.

Statistical Analysis

Descriptive statistics were generated with the SPSS computing program (SPSS, Inc, Chicago, IL). The X^2 statistic was used to test the relationship between the evaluations of the risks and the benefits on the one hand, and IRB members' final judgments on the protocol on the other. We compared the evaluations of the risks and benefits of (1) IRB members who believed the risks outweighed the benefits (n=13) with those of IRB members who believed the benefits to outweigh the risks, or who believed risks and benefits were approximately equally weighted (n=24); and (2) of IRB members who would approve the protocol without revision (n=16) with those of IRB

members who would approve the protocol after revision or who rejected the protocol (n=26). We considered using multiple regression techniques to predict the RBR and ethical acceptability of the trial, using the various specific benefits and risks as predictors. However, the statisticians we consulted advised against using such an approach due to missing data on the individual data level.

The X^2 statistic was also used for testing the relationship between professional status, length of IRB membership, age and sex, and IRB members' final judgements on the protocol. We compared the assessment of the risk/benefit ratio, and the assessment of the ethical acceptability of the protocol of: (1) physicians (n=19) versus other professionals (n=24); (2) oncology specialists (n=9) versus the other IRB members (n=34); (3) nurses (n=8) versus the other IRB members (n=35); (4) IRB members with a membership of four years or less (n=24) versus those who had a longer association with an IRB (n=19); (5) IRB members younger than 40 years (n=7) versus those 40 years of age or above (n=36); and (6) female (n=15) versus male IRB members (n=28). Multiple logistic regression analysis was used to simultaneously examine the association between the IRB members' sociodemographic and professional characteristics and their final assessments of the RBR and ethical acceptability of the protocol.

5.3 Results

Identification and estimation of risks and benefits

Inconvenience

As shown in Table 5.1, hospital admission and time investment (travel, waiting etc.) were rated as the most inconvenient aspects of trial participation: 93% and 72% of the IRB members estimated these aspects as very or fairly inconvenient. Additional examinations and extra control visits were rated by 73% and 56% of the respondents as very or fairly inconvenient.

Table 5.1: *Estimation by IRB members of the inconvenience of the phase II study for participating patients (N=43)*

	Very	Fairly	Not very	Not at all	Not applicable [a]
Hospital admission	35%	58%	7%	0%	0%
IV treatment	5%	28%	65%	2%	0%
Additional examinations	17%	56%	27%	0%	0%
Extra control visits	7%	49%	39%	0%	5%
Time investment (travel, waiting etc.)	23%	49%	23%	5%	0%

[a] Respondents could choose this alternative when they believed a certain form of inconvenience was not present in the trial.

Toxicity

Table 5.2 presents the evaluation of the most common toxicities along 5 axes: likelihood, severity, duration, reversibility and amenability to treatment. There was broad agreement among IRB members on the expected toxicity of the treatment: hair loss, diarrhea, nausea, vomiting, fatigue and organ toxicity were estimated by most IRB members as very to fairly likely. Additional toxicities expected by IRB members to be very or fairly likely were: mucositis, infection, fertility problems/damage to offspring, bleeding, change of skin color, high blood pressure, tremors, painful hands and feet, stomatitis, haematuria, genetic disturbances, and rejection of donor bone marrow. Most respondents rated these toxic effects as fairly severe to life threatening, expected hair loss and fatigue to last for some months to years, and 30% and 44%, respectively, expected organ toxicity and cognitive neurological problems to last for some months to years. Although hair loss, diarrhea, and nausea and vomiting were expected to be reversible, fatigue and organ toxicity were typically not. Also, half of the respondents expected cognitive/neurological problems to be irreversible or sometimes irreversible. Although most expected some toxic effects to be amenable to treatment, for hair loss and fatigue this was not the case. Furthermore, half of the IRB members expected organ toxicity and cognitive/neurological problems, and more than one-third other toxicity, not to be treatable. Only a small percentage of respondents did not know how to estimate the likelihood, severity, duration, reversibility and amenability to treatment of toxic effects.

Table 5.2: *Estimation by IRB members of the likelihood, severity, duration, reversibility and amenability to treatment of possible toxicity to patients during and/or after the experimental treatment (N=43)*

	LIKELIHOOD			SEVERITY				DURATION				REVERSIBILITY			AMENIBILITY TO TREATMENT		
	Very high + fairly high	Low + very low	Don't know	Mild	Fairly severe	Severe	Life threatening	Don't know	Acute* or short term	Chronic**	Don't know	Reversible	Sometimes irreversible + irreversible	Don't know	Amenable to treatment	Not amenable to treatment	Don't know
Hair loss	84%	7%	9	33	20	37	0	10	17	73	10	79	13	8	9	88	3
Diarrhea	75%	13%	12	3	63	22	2	10	86	2	12	76	17	7	93	5	2
Nausea	81%	10%	9	7	45	38	0	10	87	5	8	80	15	5	98	0	2
Vomiting	86%	3%	11	2	45	42	0	11	89	3	8	84	8	8	90	5	5
Fatigue	79%	14%	7	6	48	38	0	8	15	75	10	22	68	10	4	88	8
Organ toxicity (heart, kidney and liver)	63%	28	9	0	22	35	33	10	32	30	38	12	73	15	27	48	25
Cognitive neurological problems	37%	58	5	15	28	38	3	16	31	44	25	22	50	28	11	52	37
Other	35%	58	7	5	37	21	26	11	56	22	22	52	37	11	44	39	17

* Acute or short term = some days to some weeks

** Chronic = some months to years

Psychosocial distress

Ninety-three percent of the IRB members believed trial participation would entail psychological distress for the patient beyond that caused by the illness itself (data not presented in tabular form). As shown in Table 5.3, approximately 50% expected patients to experience depression, 79% stress, and 88% uncertainty as a result of trial participation. Other forms of psychosocial distress, such as loneliness, donor dependence, and fear were identified by 16% of the IRB members. Most respondents rated depression, stress, and uncertainty as fairly or very severe. More than one-third expected depression, stress and other manifestations of psychological distress to last for some months to years, while two-thirds expected uncertainty to last that long or longer. Most IRB members were able to estimate the likelihood, severity and duration of the psychological burden.

Seventy-two percent of respondents believed trial participation to be a social burden for the patient (not presented in tabular form). As reported in Table 5.3, two-thirds expected a strain on relationships with partners and on other social contacts. Seven percent also mentioned long periods of illness or a strain on the patient's professional life as expected stressors. Most IRB members rated the extra strain on the relationship with partners and other social contacts to be fairly severe or severe, while about half expected this to last for some months to years.

Benefits to participating patients

As indicated in Table 5.4, 40% of respondents expected tumor remission and 35% a longer symptom-free period to be fairly or very likely. Only a minority of IRB members expected that other benefits would accrue to patients (e.g., 16% longer overall survival, 14% less toxicity, 7% less pain, and 7% a better quality of life). Two-thirds of the respondents believed that trial participation would provide hope to patients. The majority of IRB members expected tumor remission, prolongation of life, a longer symptom-free period, other toxicities, and hope to last for some months to years; other potential benefits such as less toxicity than an alternative treatment (or no treatment), less pain, and a better quality of life, were expected to last only several days or weeks. Approximately two-thirds of the respondents evaluated the benefits to patients as very or fairly important and about one-third as not that important, unimportant or unknown.

Table 5.3: *Estimation by IRB members of the likelihood, severity and duration of possible extra psychosocial burden to patients during and/or after the experimental treatment (N=43)*

	LIKELIHOOD					**SEVERITY**					**DURATION**			
	Very high + fairly high	Low + very low	Don't know	* Not applicable	Did not answer question	Not severe	Fairly severe + severe + very severe	Don't know	Not applicable	Did not answer question	Acute or short term**	Chronic ***	Don't know	Not applicable	Did not answer question
Psychological burden															
Depression	51%	35%	5%	9%	0%	13%	65%	11%	11%	0%	22%	43%	24%	11%	0%
Anxiety	79%	12%	0%	9%	0%	8%	80%	2%	10%	0%	35%	40%	15%	10%	0%
Uncertainty	88%	3%	0%	9%	0%	7%	81%	2%	10%	0%	14%	64%	12%	10%	0%
Other	16%	70%	5%	9%	0%	0%	50%	17%	33%	0%	8%	42%	17%	33%	0%
Social burden															
Extra strain on relationship with partner	61%	9%	2%	28%	0%	3%	62%	5%	30%	0%	8%	45%	17%	30%	0%
Extra burden other social contacts	63%	7%	2%	28%	0%	7%	58%	7%	28%	0%	5%	49%	18%	28%	0%
Loss of prestige	5%	60%	7%	28%	0%	29%	10%	22%	39%	0%	7%	13%	40%	40%	0%
Other	7%	63%	2%	28%	0%	0%	25%	0%	75%	0%	0%	25%	0%	75%	0%

* Not applicable = percentage of IRB members that did not expect extra psychosocial burden to patients or did not know this; they did not answer the questions about the likelihood, severity and duration of extra psychosocial burden to patients. **Acute or short term = some days to some weeks.
*** Chronic = some months to years

Table 5.4: *Estimation by IRB members of the likelihood, duration and importance of the possible benefits of the experimental treatment to the participating patients (N=43)*

		LIKELIHOOD				DURATION				IMPORTANCE		
	Very high + fairly high	Low + very low + zero	Don't know	Did not answer question	Some days to some weeks	Some months to years	Don't know	Did not answer question	Very large + fairly large	Very little +fairly little	Don't know	Did not answer question
Tumor remission	40%	41%	9%	0%	7%	63%	30%	0%	62%	30%	8%	0%
Prolongation of life	16%	75%	9%	0%	11%	62%	27%	0%	69%	26%	5%	0%
Longer symptom-free period	35%	58%	7%	0%	17%	59%	24%	0%	71%	24%	5%	0%
Less toxicity than alternative treatment	14%	72%	21%	0%	24%	16%	60%	0%	62%	19%	19%	0%
Less pain	7%	72%	21%	0%	16%	28%	56%	0%	65%	19%	16%	0%
Better quality of life	7%	72%	21%	0%	7%	43%	50%	0%	65%	19%	16%	0%
Hope	65%	28%	7%	0%	11%	64%	25%	0%	58%	31%	11%	0%
Other	7%	93%	0%	0%	0%	67%	33%	0%	67%	0%	33%	0%

Benefits to future patients and science

Sixty-eight percent of the IRB members were unable to estimate how many patients in the Netherlands would benefit annually from the experimental treatment, should it prove effective. Most members rated the clinical trial as fairly to very important (8% of very great importance, 39% of great importance, 39% of moderate importance).

Evaluation of specific risks and benefits, assessment of the risk/ benefit ratio, and ethical acceptability of the protocol

Evaluation of risks and benefits

The possible advantages and disadvantages of the experimental treatment to the patients were rated as fairly or very important by 63% and 91% of the IRB members, respectively. The importance of the trial to future patients and science was rated as high by 23% and 10%, respectively (Figure 5.1). Although nearly all (98%) of the respondents rated toxicity as the most important risk of the trial treatment, they also evaluated the inconveniences and the psychological burden to patients as very or fairly important in their risk/benefit assessment of the trial.

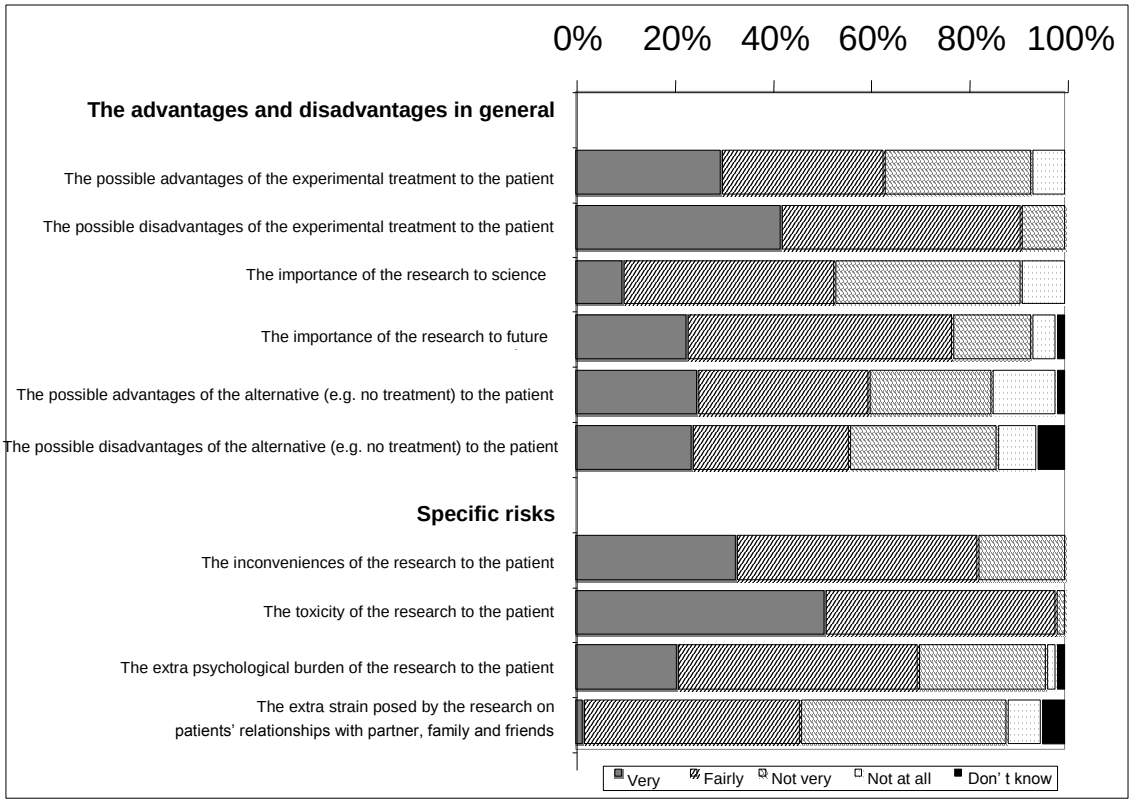

Figure 5.1: *The weight given by IRB members to different advantages and disadvantages*

of the phase II study (N=43)

Final assessment of the risk/benefit ratio (RBR) and the ethical acceptability of the research

Thirty percent of the IRB members believed that the risks of the protocol outweighed the benefits, 21% believed that the benefits outweighed the risks, and 35% assigned approximately equivalent weights to the risks and benefits (not in tabular form). Thirty-seven percent of the IRB members would approve the protocol and 44% would recommend approval following revision. Although 44% of the IRB members believed that the risks outweighed the benefits or were unable to evaluate the risk/benefit ratio, only 18% would reject the protocol or could not judge its ethical acceptability. There was a significant relationship between the assessment of the RBR and of the ethical acceptability of the trial ($p < .031$). Most of the IRB members (83%) who believed that the risks of the protocol outweighed the benefits, would reject the protocol; 17% of them would approve the protocol or would approve following revision. More than half (54%) of the IRB members who believed the benefits outweighed the risks or who assigned approximately equivalent weights to the risks and benefits, would approve it; less than half would reject it or would approve following revision.

Differences in assessment

Differences in overall assessment of the RBR and the ethical acceptability as a function of ratings of specific risks and benefits

There were a number of significant associations observed between the assessment of specific risks, and particularly the duration of such risks, and the overall RBR assessment (Table 5.5). The ratings of the inconvenience and benefits of the treatment to participating patients had no or only limited effect on the overall RBR assessment (Tables 5.5 and 5.6). Importance of tumor remission was related to the RBR assessment, and duration of tumor remission and duration of a symptom-free period, were significantly related to both the assessment of the RBR and the ethical acceptability of the trial. IRB members who believed that the risks outweighed the benefits rated the organ toxicity and cognitive/neurological problems to be significantly more likely, hair loss, diarrhea, nausea, vomiting and organ toxicities to be of longer duration, cognitive and neurological problems to be more often irreversible, and the burden of treatment on social contacts to be more severe and of a longer duration.

Table 5.5: *Relationship between the various risks and benefits and the assessment of the RBR of the phase II study (N=43)* [a]

	RBR		sign.
	risks outweigh benefits	**benefits outweigh the risks or risks and benefits weigh nearly the same**	
Possible toxicity			
likelihood of organ toxicity			.003
very high	70%	14%	
fairly high	30%	46%	
low	0%	40%	
very low	0%	0%	
likelihood of cognitive neurological problems			.018
very high	50%	4%	
fairly high	20%	23%	
low	20%	32%	
very low	10%	41%	
duration of hair loss			.018
some days [b]	0%	0%	
some weeks	33%	13%	
some months	44%	87%	
years	23%	0%	
duration of diarrhea			.034
some days	22%	68%	
some weeks	67%	32%	
some months	11%	0%	
years	0%	0%	
duration of nausea			0.22
some days	22%	61%	
some weeks	44%	39%	
some months	22%	0%	
years	12%	0%	
duration of vomiting			0.10
some days	22%	74%	
some weeks	44%	26%	
some months	12%	0%	
years	22%	0%	
duration of organ toxicity			0.35
some days	11%	24%	
some weeks	11%	41%	
some months	22%	29%	
years	56%	6%	
reversibility of cognitive neurological problems			.009
reversible	13%	46%	
sometimes reversible, sometimes not reversible	25%	54%	
irreversible	62%	0%	

	RBR		sign.
	risks outweigh benefits	**benefits outweigh the risks or risks and benefits weigh nearly the same**	
severity of extra burden on other social contacts			.037
not severe	0%	7%	
fairly severe	43%	86%	
severe	57%	7%	
very severe	0%	0%	
duration of extra burden on other social contacts			.025
some days	0%	0%	
some weeks	33%	0%	
some months	33%	92%	
years	34%	8%	
Benefits			
duration of tumor remission			.034
some days	13%	0%	
some weeks	25%	0%	
some months	62%	57%	
years	0%	43%	
importance of tumor remission			.002
very important	0%	32%	
fairly important	13%	47%	
not so important	37%	21%	
unimportant	50%	0%	

[a] Only the significant relationships are presented in the Table; for instance there is no significant relationship between the inconvenience of the trial and the RBR assessment.

[b] Some days or some weeks= acute; some months to years = chronic

Table 5.6: *Relationship between the various risks and benefits and the assessment of the ethical acceptability of the phase II study (N=43)* [a]

	ethical acceptability		
	approve	**needs revision or reject**	**sign.**
Benefits			
duration of tumor remission			.032
some days	0%	6%	
some weeks	0%	12%	
some months	44%	76%	
years	56%	6%	
duration of symptom free period			.032
some days	0%	7%	
some weeks	28%	13%	
some months	36%	80%	
years	36%	0%	

[a] Only the significant relationships are presented in the Table.

Differences in assessment by IRB members' characteristics

Physicians did not differ significantly from other professionals in the assessment of the risk/benefit ratio and of the ethical acceptability of the protocol. This was also true for oncologists compared to other IRB members. Nurses, however, differed significantly from other IRB members in their assessment of the ethical acceptability of the protocol, as can been seen in Table 5.7.

Relatively new IRB members (membership of four years or less) were significantly more likely to approve the protocol, or recommend approval after revision, than members who had a longer association with an IRB. Length of IRB membership did not correlate significantly with the RBR assessment of the protocol.

Older IRB members (>= 40) differed significantly in their RBR assessment from younger members: they more often considered the risks to outweigh the benefits (37% versus 0%) or the benefits to outweigh the risks (23% versus 0%), and less often found risks and benefits to weigh nearly the same (29% versus 71%) or believed that they could not answer the question (11% versus 29%) (p = .038). They were also more likely to approve the protocol (43% versus 14%) or recommend rejection (20% versus 0%), and less likely to recommend approval following revision (34% versus 86%) than younger members (p= .047).

Table 5.7: *Relationship IRB members' characteristics and assessment of the RBR and ethical acceptability (N=43)* [a]

	professional status		**sign.**	**length of membership**		**sign.**	**age**		**sign.**	**gender**		**sign.**
	nurses	other profes-sionals		<= 4 years	> 4 years		< 403	>= 40		female	male	
RBR assessment									.038			
risks outweigh benefits							0%	37%				
risks and benefits weigh nearly the same							71%	29%				
benefits outweigh risks							0%	23%				
don't know							29%	11%				
Assessment of the ethical acceptability			.027			.041			.047			.005
approve	13%	43%		46%	26%		14%	43%		7%	54%	
revise	87%	34%		50%	37%		86%	34%		73%	28%	
reject	0%	20%		4%	32%		0%	20%		13%	18%	
don't know	0%	3%		0%	5%		0%	3%		7%	0%	

[a] Only the significant relationships are presented in the Table.

Significant gender differences were also observed with respect to the assessment of the ethical acceptability of the trial protocol. Female IRB members were significantly less likely to approve the protocol (75 versus 54%), and were more likely to recommend approval following revision (73% versus 28%) than were their male counterparts. There were no significant differences in the RBR assessment of male and female IRB members.

When including all IRB members' characteristics in a multiple logistic regression analysis, only gender was associated significantly with the assessment of the ethical acceptability of the trial. Female members were significantly more likely to reject the protocol or to recommend approval after revision than males ($p < .014$). There were no significant relationships found in a multiple logistic regression for all IRB members' characteristics and the RBR assessment.

5.4 Discussion

The aims of the current study were to examine how individual IRB members assess the diverse risks and the benefits of a specific phase II cancer protocol, and to examine how they come to their final assessment of the risk/benefit ratio and of the ethical acceptability of the proposed trial. First, we were interested in determining what type of risks and benefits IRB members identify in evaluating a particular Phase II cancer protocol, and how they estimate and evaluate these risks and benefits. The results indicate that most IRB members felt competent to estimate specific aspects of the risks and benefits such as likelihood and severity –although the expected duration of such risks and benefits proved more difficult to evaluate–, to determine the RBR, and to assess the ethical acceptability of the trial. These findings are consistent with those reported previously for IRB members' estimations for phase II cancer protocols, in general (Van Luijn, 2000; Van Luijn et al. 2002).

The results also indicate that, besides inconvenience and fairly severe to sometimes life threatening physical risks (toxicity), IRB members identified several serious psychological and social risks of trial participation. This is in line with the distinction made by Levine between different kind of risks in medical experiments for participating patients (physical, psychological, social) in medical experiments (Levine, 1986). Although psychological and social risks were given less weight than inconvenience or toxicity, 46% and 70% of the respondents attached very heavy to fairly heavy weights to these risks in their risk/benefit assessment of the protocol. The results further indicate that, while IRB members believed the research to be important, they expected only modest benefits to accrue to the participating patients. Although a substantial percentage of IRB members rated benefits to patients such as tumor remission (40%) a longer symptom-free period (35%), and hope (65%) to be fairly or very likely, only a few expected this to be the case with respect to prolongation of life, reduction in pain, less toxicity than an alternative treatment (e.g. no treatment) and a better quality of life.

Second, we investigated the IRB members' evaluation of specific risks and benefits, the assessment of the risk/benefit ratio and the ethical acceptability of the protocol. Although IRB members reported that the possible disadvantages of the experimental treatment to participating patients were the most important factors to consider in the RBR assessment (more important than benefits to participating patients, future patients or medical science), most believed that the benefits outweighed the risks, or that risks and benefits had a nearly equal weight, and most wanted the trial to take place. Furthermore, as one would expect, a significant association was observed between the assessment of the RBR and the assessment of the ethical acceptability of the trial; that the IRB members' evaluation of the RBR plays a significant role in their final decision regarding the ethical acceptability of the trial.

Third, we investigated the relationship between the various specific risks and benefits, and the assessment of the trial's RBR and the final judgment on its ethical acceptability. Several significant relationships were found between the assessment of (aspects of) particular risks and benefits, and the RBR assessment, especially between the assessment of the duration of several risks and the RBR assessment. As to the benefits, only duration and importance of tumor remission were significantly related to the assessment of the trials' RBR and duration of tumor remission and a symptom-free period to its ethical acceptability. Apparently, the IRB members' RBR assessment is mainly based upon weighing the duration of certain risks against the benefits of tumor remission and of symptom-free survival. The final judgment on the trial's ethical acceptability is even only significantly correlated to the benefits of the duration of remission and symptom free survival. Most cancer patients, however, participate in trials because they hope for a treatment effect in terms of prolongation of life (Daugherty et al., 1995; Schaeffer et al., 1996; Miller, 2000). Because we did not study the letter of informed consent, we cannot say what patients were told about their benefit in the trial. However, it can be doubted, considering (1) that patients themselves have to carry the risks and (2) the weight they assign to prolongation of life, whether patients having the same information as the IRB members, would come to a RBR assessment, similar to that of IRB members. At the one hand this observation underlines the need to be open and honest in informing the patients, at the other hand it provides a very strong argument for taking the perspectives of patients into account when determining the RBR of trials.

Fourth, we investigated whether there were systematic differences in assessment of the risk/benefit ratio and the ethical acceptability of the protocol as a function of the professional background, number of years of committee experience, age and gender of IRB members. Physicians and non-physicians did not differ significantly in their assessment of the risk/benefit ratio or of the ethical acceptability of the protocol. The same was true for oncology specialists compared to other IRB members. Apparently there is less difference between medical and non-medical IRB members with respect to

the content of their RBR-assessment than with respect to difficulty in making this assessment. An earlier study found that non-medical IRB members find RBR-assessment more difficult than medical IRB members (Berghmans et al, 1996; 1997). However, nurses, members with a longer association with an IRB, and female IRB members were more critical in their evaluations than other professionals, relatively new members, and male IRB members. Older IRB members (> 39) were more extreme in their RBR assessment (more often believed that risks outweigh the benefits or vice versa) and in their assessment of the ethical acceptability (more likely to approve or disapprove the protocol and less likely to recommend approval following revision) than younger members. It is possible that members with a longer association with an IRB are better able to compare the protocol with other protocols or that they are better informed about the risks and benefits of the trial to patients. Nurses and female IRB members may be more critical because they can more easily identify themselves with breast cancer patients based on their professional experience or simply because they are women themselves. In a multivariate analysis including all of the IRB members' sociodemographic and professional characteristics, only gender was found to be associated significantly with the assessment of the ethical acceptability of the protocol, with female members being significantly more likely to reject the protocol or to recommend approval after revision than males ($p < .014$). This suggests that it may be important to maintain a gender balance in IRB membership, as it appears that women may bring a different perspective to the RBR assessment process than their male counterparts.

A number of the study's limitations should be mentioned. First, we only evaluated one specific phase II cancer protocol. Although it would have been preferable to ask the IRB members to evaluate a range of protocols, this was not feasible given the rather labor intensive nature of the research. We believe that the trial protocol that we selected for review was reasonably representative of phase II cancer clinical trials in general, although, as we stated earlier, the treatment schedule was quite intensive.

Second, the participants in this study were all drawn from the IRBs of Dutch academic hospitals or specialized cancer centers. Whether our results can be generalized to other types of hospitals or to other countries is uncertain. The settings in which European and American IRBs operate may differ in certain respects. For example, in the U.S. there is generally a greater concern with protecting hospitals and physicians from possible legal action than is the case in Europe. However, the structure, objectives and procedures of IRBs are similar, regardless of whether they are American or European. Thus we are fairly confident that our results can reasonably be extended to IRBs, in general.

Finally, we would note that our study was based on questionnaire data rather than observational data, and that we queried individual IRB members rather than investigating the IRBs as a whole. We realize that the decisions taken by IRBs are often collective ones, and emerge from discussions and debates that take place during IRB

meetings. Nevertheless, each IRB member brings his or her own perspective to such deliberations, and is expected to be well prepared to participate actively in the decision making process. Thus it is not inappropriate to examine the attitudes and behavior of individual IRB members. At the same time, we would recognize the value of other types of research (e.g., observational studies) that would better be able to capture the group dynamics involved in IRB decision making. In a future paper, we will report the results of a latter stage of the current study in which such observational techniques were employed.

In summary: First, most IRB members estimated hope (a psychological benefit) to patients as as important as physical benefits (about 60% believed physical benefits to be fairly or very important, see table 5.4), but more likely (65% believed hope to be fairly or very likely versus 7-40% the physical benefits, see table 5.4). Hope is, of course, important. Although we did not study why patients want to participate in clinical trials, the literature learns that most patients participate hoping that this will prolong their lives (Miller, 2000). This hope is in danger of becoming irrational if the chances for survival are very low. On the one hand we observe that IRB members consider, in contradistinction to tumor remission and a longer symptom-free period, survival benefit to be unlikely. On the other hand they regard the psychological benefit of hope as important as physical benefits in their RBR assessment. If hope is an almost illusionary benefit, is it ethically acceptable to include it in assessing the RBR? We know from earlier studies that patients' and medical doctors' expectations of benefit of participation in medical experiments is different (Daugherty et al., 1995). It would be an improvement if patient information sheets pay more attention, as they normally do to the risks, to the possible benefits to participating patients. For example they should contain more detailed information about the likelihood of prolongation of life. This would prevent patients' hope to become irrational.

Second, although IRB members found the possible disadvantages of the experimental treatment to participating patients the most important factors to consider in the RBR assessment (more important than benefits to participating patients, future patients or medical science), and although they evaluated the risks to be fairly severe to sometimes life-threatening, most believed that the benefits outweighed the risks, or that risks and benefits had a nearly equal weight, and most wanted the trial to take place. Their final judgment on the trial's ethical acceptability is only significantly correlated to the benefits of the duration of remission and symptom free survival and not to the risks or the other studied benefits to participating patients.

Appendix: *Parameters studied in survey of phase II cancer protocol*

Identification and estimation of inconvenience for the research subjects
"How burdensome do you think this situation is for the patient?" Admission of the patient to the hospital, IVs, extra examinations, extra control visits and time investment (travel, waiting etc.). *

Identification and estimation of toxicity for the research subjects
"What kind of toxicity you believe would happen during and/or after the research?"(one could choose between hair loss, diarrhea, nausea, vomiting, fatigue, organ toxicity, cognitive neurological problems or still other toxicity) †
"Indicate the likelihood, severity, duration, reversibility and amenability to treatment for the subject during and/or after experimental treatment of the following: hair loss, diarrhea, nausea, vomiting, fatigue, organ toxicity, cognitive neurological problems or still other toxicity. ‡

Identification and estimation of psychosocial distress for the research subjects
"Do you believe participation in the experimental treatment will impose an extra psychological burden (beyond the burden imposed by the illness and previous treatment) for the patient?" §
"Do you believe participation in the experimental treatment will place an extra social burden (beyond the social burden imposed by the illness and previous treatment alone) on the patient?" §
"Indicate the likelihood, severity and duration of the following psychosocial stress for the subject during and/or after the experimental treatment as an extra psychological and social burden (over and above the stress related to the illness and treatment): depression, stress, uncertainty, extra strain on relationships with partners, extra strain on other social contacts and loss of prestige. ¶

Identification and estimation of benefits to the research subjects
"What kind of benefits to participating patients you believe would happen during and/or after the research?"(one could choose between tumor remission, prolongation of life, longer symptom-free periods, less pain, better quality of life, and hope or still other benefits) ** "Indicate the likelihood, duration, and importance of the following benefits for the subject during and/or after experimental treatment: tumor remission, prolongation of life, longer symptom-free periods, less toxicity than alternative treatment, less pain, better quality of life, hope or still other benefits." ††
Identification and estimation of benefits to future patients and medical science
"Indicate how many patients would benefit every year in the Netherlands from the experimental treatment should it prove effective."
"Indicate the importance of the research study." ‡‡

Evaluation of risks and benefits
"How important in your risk/benefit ratio assessment are the following advantages and disadvantages: the possible risks and benefits of the experimental treatment to the patient, the importance of the study for future patients and science, the possible risks and benefits of the alternative to the patient, inconveniences, toxicity, extra psychological stress and extra strain on the patient's relationships with his/her partner, family and friends. § §
The RBR assessment of the study
"What is your final assessment of the risk/benefit ratio of the study?" ¶ ¶
The assessment of the ethical acceptability of the study
"What is your final assessment of the study?" ***

* Answers were scored on a 4-point Likert scale from ‘very burdensome’ to ‘not burdensome at all’.

† If a certain kind of toxicity was believed not to happen, this answer was scored as an answer to the next question concerning the likelihood of the toxicity as that the likelihood would be ‘not high at all’. If the toxicity was believed to happen, the respondent was asked how he estimated the likelihood of this toxicity and his answer was also scored as an answer to the next question concerning the likelihood of the toxicity.

‡ Answers were scored on a 4-point Likert scale from: (1) ‘very high’ to ‘not high at all’; (2) ‘mild’ to ‘life threatening’; (3) ‘a few days’ to ‘years’; (4) ‘reversible’ to ‘irreversible’; and (5) ‘amenable to treatment’ to ‘not amenable to treatment’.

§ Answers were scored as: (1) yes, (2) no, (3) don’t know.

¶ The question was scored on a 4-point Likert scale from (1)‘very high’ to ‘not high at all’; (2) ‘not so severe’ to ‘very severe’; (3) ‘a few days’ to ‘years’.

** If a certain kind of benefit was believed not to happen, this answer was scored as an answer to the next question concerning the likelihood of the benefit as that the likelihood would be ‘not high at all’. If the benefit was believed to happen, the respondent was asked how he estimated the likelihood of this benefit and his answer was also scored as an answer to the next question concerning the likelihood of the benefit.

†† Answers were scored on a 4-point Likert scale from (1) ‘very high’ to ‘not high at all’; (2) ‘a few days’ to ‘years’; (3) ‘very important’ to ‘not important at all’.

‡‡ The first question was an open question; answers to the second question were scored on a 4-point Likert scale from ‘very important’ to ‘not important at all’.

§ § Answers were scored on a 4-point Likert scale from ‘very important’ to ‘not important at all’.

¶ ¶ Possible answers included: (1) ‘the risks outweigh the benefits’; (2) ‘the benefits outweigh the risks’; (3) ‘the risks and benefits weigh approximately the same; or (4) ‘don’t know’.

*** Possible answers included: (1) ‘approve’, (2) ‘needs revision’, (3)‘reject’ and (4) ‘don’t know’.

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*6 Can IRBs assess the heterogeneous and incommensurable risks and benefits of research protocols?**

Summary

Institutional review boards (IRBs) are legally required to determine whether the relation between the risks and benefits of a proposed study is reasonable. There are reasons to doubt whether the decisions of IRBs about risks and benefits are the result of a process of systematic comparison and weighing. It is argued that, even if there was sufficient information on which to make such decisions, and even if a normative consensus about how to categorize and assess the risks and the benefits of a study were available, it would still be very difficult, if not impossible to make an objective or neutral assessment of the ratio between risks and benefits due to their heterogeneous and incommensurable nature. The necessity and possibility of revising or reinterpreting the legal requirements surrounding the work of IRBs, or of rethinking the tasks that IRBs are required to carry out, are discussed.

6.1 Introduction

The Dutch law on Medical Experiments Involving Human Subjects of 1998 states in article 3c that an Institutional Review Board (IRB) can only approve a research protocol "if it can reasonably be expected that the interest to be served by the research is proportional to the burdens and risks for the research subject". Article 3g states that it should be clear from the protocol "to what extent the research subject can benefit from the research". Many other countries have regulations

specifying similar conditions for the approval of medical research by an IRB. For example, in the U.S. the 'Common Rule' states at 45 cfr 46.111a(2) that IRBs must determine "that risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result". The Common Rule requires at 45 cfr 46.116(3) that participants should be provided with "a description of any benefits … which may reasonably be expected from the research." Although the wording in the Dutch law is different from that in the Common Rule, both presuppose it to be possible to determine that the burdens and risks are proportional to the interest to be served by the research (the Dutch law) or reasonable in relation to the anticipated benefits for the human subject, together with the importance of expected knowledge resulting from the research (the Common Rule).[i] In recent years, various publications have signalled the problems, both in theory and in practice, associated with determining the reasonableness of the burdens and risks of participating in medical research in relation to the benefits to subjects or to

* A.W. Musschenga, H.E.M. van Luijn, N.K. Aaronson & R.B. Keus. Submitted to IRB: Ethics and Human Research.

society (Levine, 1978; Meslin, 1989; Martin et al., 1995; King, 2000). The main problems are: 1) There are limits to the information available to IRBs and research subjects for assessing the reasonableness of risks in relation to benefits; 2) A normative consensus about how to categorize and assess especially the benefits of a study is lacking;[ii] 3) Because of the heterogeneous and incommensurable nature of both the risks and the benefits, an objective assessment of whether the relation between risks and benefits is reasonable is very difficult or even impossible to make.[iii]

The first problem, the incompleteness of the available information, makes it difficult to determine the ratio between risks and benefits (RBR) of a treatment. However, the problem is not specific for RBR-assessments, but is common to many medical decisions. In our view, the second difficulty, the lack of a normative consensus about how to categorize and assess not only the risks but also the benefits of a study, can be solved. Authors such as Meslin, Levine and King have made important contributions to developing a conceptual framework for describing and assessing risks and benefits.[iv]

Our focus in this article is upon the third problem which, in our view, is the most difficult one. The heterogeneous and incommensurable nature of both the risks and the benefits of a study makes an *objective* assessment of its RBR very difficult or even impossible. By objective assessment we mean an assessment from what Nagel would call an objective, neutral, perspectiveless point of view (Nagel, 1986). In assessing the RBR of a study, IRBs need to agree upon the relative weight attached to specific risks and benefits. However, one cannot assign weights to risks and benefits without adopting a particular perspective, consisting of certain (moral) background values. Thus, in order to come to an agreement on the RBR, IRB members need to have a certain consensus on these background values and their ordering. Other IRBs or patients who do not share this view on values and their

ordering, may come to a different judgment about the reasonableness of risks in relation to benefits.

This observation has important consequences for the work of IRBs. IRBs are legally required to determine whether the relation between the risks and benefits of a study is reasonable. If their judgments are so much influenced by their moral background values, what relevance and importance should be attached to them? RBR-assessment of IRBs do have consequences. Although patients, in considering whether to participate in a study, make their own final decisions, the knowledge that the study has been reviewed and approved by an IRB does play a role in their deliberations (Madsen et al., 2000). However, if patients do not know the values underlying an assessment, they are in danger of being misled. In our view IRBs cannot meet the normative expectations implied in current laws and rules of diverse countries. The problem of the incommensurability of risks and benefits, together with the two other issues noted above, results in IRBs being unable to determine objectively whether the relation between risks and benefits is reasonable. What they actually do when assessing RBR is ensure, on the one hand, that a proposed study does not present unacceptable risks for patients and, on the other, that the study has some potential to benefit them and/or future patients. However, this is not what is meant by assessing whether the ratio between risks and benefits is reasonable or proportional. Thus, the actual practice of IRBs in reviewing a study protocol does not meet what the legal rules demand from them.

There are several possible ways to close the gap between legal demands and actual practice. One possibility is to adjust the legal rules to the actual practice by reformulating the tasks of IRBs. In the revised form the main task of an IRB would be to 1) judge the scientific validity and importance of the research, 2) identify and estimate the diverse risks and benefits, 3) determine whether the risks are reasonable and whether the research has the potential to benefit the research subjects and/or future patients and 4) check the correctness and completeness of the information provided to patients. This task can only be satisfactorily executed if the protocol contains sufficient information on the scientific value of the research, and other benefits and risks. In this formulation IRBs would not be required to make a complete and comprehensive judgement about the reasonableness of the relation between risks and benefits. That judgment would be left to the potential research subjects.

A second approach to closing the gap between actual practice and legal rules would be an authoritative (re)interpretation of the rules. This would involve a judicial body or other legal institution changing the legal requirement to determining whether the risks are acceptable and whether the research has the potential to benefit the research subjects and/or future patients. A third approach would be to ensure that the actual practice of IRBs conforms more closely to the current rules.

In this article we reflect upon the findings of a four-stage research project on the assessment of the risk/benefit ratio of experimental treatments in oncology by IRBs. Experimental treatments in oncology differ from other experimental treatments in that the risks associated with the treatments are often quite serious. The difficulties in determining the ratio between risks and benefits are therefore more prominent in clinical oncology than in other medical fields. In section 6.2 we argue

that, because of the heterogeneous and incommensurable nature of both risks and benefits, an objective assessment of the relative weight of risks and benefits, and thereby of the proportionality of their relation, is very difficult if not impossible. In section 6.3 we report on our research project. We conclude from this research that the judgments of IRB-members on the proportionality (reasonableness) of the risks of a research in relation to the potential benefits have only limited relevance for patients considering participation in a trial and may even give them a false impression of what they can expect from participating. In section 6.4 we discuss further the three potential means of closing the gap between the actual practice of IRBs in reviewing research protocols and what the legal rules require them to do.

6.2 Is an objective assessment of the reasonableness of the risk/benefit ratio possible?

IRBs are not only obliged to check whether the risks and benefits of a study are clearly explained in the patient consent forms, in a language understandable to an average patient. They also have to determine whether the risks for the research subject are reasonable in relation to the potential benefits. Under the current regulations in countries such as the Netherlands and the U.S., this should be done before a study can be approved; thus, before asking potential research subjects to participate. This obligation is not covered by the principle of respect for autonomy, but follows from the principle of non-maleficence. IRBs should protect research subjects against the risks of harm that are not balanced by potential benefits. This is the rationale behind RBR assessments. The principle of respect for autonomy only demands that investigators provide complete information about the risks and benefits of a study to potential research subjects, to enable them to make an autonomous and informed decision about participation in a trial. The principle of non-maleficence precedes that of respect for autonomy. This is an important point since many people wrongly assume that all the current tasks of IRBs flow from the principle of respect for autonomy.

Which arguments do we have for stating that an objective assessment of the RBR of a study is difficult if not impossible because of the heterogeneous and incommen- surable nature of both its risks and benefits? Incommensurability is a complex phenomenon which needs clarification. Suppose that you have a discussion with a friend about the attractiveness of two career options, say, that of professor and that of manager. Considering the required talents and education, both options are open to both of you. The overriding value with respect to which you want to compare the options is their satisfactoriness; their contribution to a rewarding and satisfactory life.[v] In determining how satisfactory one option is versus the other, requires one to reflect upon a number of issues or criteria, including income, autonomy, status, fame, social value, excitement, variation, and so on. These values refer to different ways in which a career can be “good.” Let us assume that at least

some of these values are incommensurable. Calling values incommensurable means that each of these values is neither more nor less valuable than others, but that they are also not equal. In other words, there is no objective point of view from which a ranking of these values can be made. You and your friend might agree that one career is better than the other with respect to some of these criteria, while being unable to reach a consensus about the overall quality of the two careers. This is what Lukes calls 'overall incommensurability' (Lukes, 1991: 34).

> ***All of us, from time to time, in our personal lives, are confronted with a choice between incommensurable options. Such a choice need not be arbitrary. Several authors argue that a justifiable choice between incommensurable options can be made by answering the question: What kind of a person am I or do I want to be and what kind of a life do I want to have? (Kekes, 1993; Taylor, 1985). Taylor characterises what a person must do in such a situation as to 'make the incommensurable commensurable'. A comparison always presupposes a specific point of view. In classical utilitarianism one makes a choice between alternatives by measuring their relative value on a certain scale, using a common denominator such as well-being or happiness. The choice is then made from an impersonal point of view. What Taylor means is that in a situation of choice between incommensurable options, commensuration has to take place, not from an allegedly 'objective' point of view, but from the particular, subjective point of view of the agent himself. Lukes calls this 'specific commensurability' (Lukes, 1991: 48-49). When reflecting upon several career options, it is often not clear to an individual which direction he wants his life to take. It does not help him to focus upon the intrinsic merits of the respective options. He has to determine for himself whether, for example, to become a professor or a manager fits into the kind of life he wants to live. A career not only consumes a great deal of your time and energy, it also influences the kind of person you become and need to become. The virtues of a good professor are not the same as those of a good manager. To choose a career is to discover what is important for you, which of your talents you want to develop. If you and your friend do not share the same subjective point of view, you will not agree about the overall quality of the two career options.***

The above example can help us in clarifying what IRBs have to do in assessing the reasonableness of the relation between the risks and the benefits of a study. When we say that the risks and benefits of a study are incommensurable we mean, first, that the values associated with risks on the one side and benefits on the other are incommensurable, and, second, that the diverse benefits are incommensurable. The category of risks comprises diverse issues such as inconveniences, and physical, psychological, social and economic harms; that of benefits comprises benefits to patients participating in the research (less pain, tumor remission, survival, higher quality of life), scientific benefits (increase of knowledge about the effects of diverse treatments), and social benefits (benefits to future patients, to their families, to society). Both risks and benefits affect diverse domains of health status. Additionally, benefits accrue to diverse stakeholders: the research

subjects, future patients, and medical science. Thus, we are confronted with two types of incommensurability: intrapersonal and interpersonal.

A further complication in assessing the reasonableness of risks in relation to benefits is that there is usually more known about the (nature, extent, and probability of) risks than about the (nature, extent and probability of) benefits. A last point is that, in making an RBR-assessment, IRBs cannot confine themselves to the experimental treatment; they also have to take the context into account. What alternatives are available for patients? In phase-II studies, designed to provide initial information about the effectiveness of a treatment, there are often no alternatives. For patients who are asked to participate in phase-III studies, designed to determine whether a new treatment is superior to a standard one, the standard treatment is always available, even outside the context of the study. Thus, the assessment of the RBR of a study will take place against the background of the available alternatives and their risks and benefits.

Let us assume that the IRB consists of highly competent and experienced members. Let us also assume that they share a conceptual framework for describing risks and benefits, and have sufficient information for identifying the risks and benefits of the study. To assess the reasonableness of the relation between the risks and the benefits of an experimental treatment, an IRB has to weigh the risks against the benefits. As was the case in our example of career options, the incommensurable can only be made commensurable by taking a particular point of view. This point of view consists of certain values, goals, beliefs about the value of (the prolongation of) life and its quality, and other ('altruistic') values. Although IRB members may differ as to these values, goals and beliefs, the obligation to make statements about the RBR of the studies they are reviewing induces IRBs to develop a – usually implicit – common view which is acceptable to all members. This explains why IRBs usually, at least in the more familiar, less complex cases, succeed to agree on the RBR of a study. The consensus or compromise on these values, goals and beliefs may be purely local. Other IRBs may have different views. This may partly explain the diversity in RBR assessment between IRBs which has been observed by several authors (Foster, 1995; Churchill et al., 2003).[vi] More important is the possible difference in point of view between the IRB and the potential research subjects. Thus, when an IRB assesses the relation between the risks and the benefits of a study as reasonable, one always has to ask: reasonable from which/whose point of view? Other studies confirm our view that extra-scientific, factors such as value judgments or attitudes towards risks, play an important role in assessing the weight attached to risks and benefits.[vii]

6.3 The risk benefit assessment of cancer clinical trials by IRB members

The problem of the heterogeneity and incommensurability of risks and benefits may be most prominent in oncology clinical trials. This was one of the main reasons for examining in more detail how IRB members assess the risk/benefit ratio and ethical acceptability of experimental treatments in oncology. We designed a study that was divided into four interrelated stages: 1) semi-structured interviews

with 53 IRB members to determine their attitudes, beliefs and experiences in evaluating the RBR of phase II clinical trials, in general, 2) evaluation of a phase II and a phase III clinical trial protocol by 43 and 41 of those members respectively, 3) in-depth interviews with IRB members about those specific protocol evaluations, and 4) observation and analysis of IRB meetings. The results from the first through fourth stages of this investigation have been published (Van Luijn, 2000; Van Luijn et al., 2002) or will be reported in subsequent articles.

We will only summarize here those findings that are relevant to the subject matter of this article. In the first stage of our research we investigated four aspects of the risk-benefit assessment process: 1) identification of the risks and benefits of phase-II clinical oncology trials, 2) estimation of the amount of information needed to make a risk-benefit assessment and whether such information is available in phase-II clinical oncology trials, 3) self-reported competence of IRB members to make a risk-benefit assessment and 4) evaluation of specific risks and benefits for patients participating in phase-II clinical oncology trials, for future patients, and for medical science. The results of this first stage of our research indicated that the absence of criteria and uncertainty about the benefits to patients and the rationale of the study make RBR assessments of cancer clinical trials difficult for many IRB members. Moreover, most IRB members expressed a desire to receive additional information and education in assessing the RBR of such trials. This finding suggests that the IRB members lack criteria for decision making about the risk benefit ratio of those protocols.[viii] Another relevant finding from this stage of the research was that between one-quarter and one-third of the respondents indicate that the clinical trial protocols provide insufficient information regarding the likelihood, magnitude and duration of both the risks and benefits. Few members reported weighing risks and benefits in a systematic manner, but rather relied on global impressions or preferred to leave such matters to the IRB as a whole or to their patients (Van Luijn et al., 2002).

The main conclusions of the second stage of the study, in which a specific phase II breast cancer protocol was evaluated by 43 IRB members were:[ix] 1) Most IRB members felt competent to estimate specific aspects of the risks and benefits, such as likelihood and severity, to determine the RBR, and to assess the ethical accetability of the trial. 2) Although IRB members stated that they attach a heavy weight to the risks, their final judgment on the trial's RBR and ethical acceptability was significantly correlated only with the benefits (specifically, the duration of tumor remission and symptom free survival) to participating patients. Most cancer patients, however, participate in trials because they hope for a treatment effect in terms of prolongation of life (Daugherty et al., 1995; Schaeffer et al., 1996; Miller, 2000). Thus, considering 1) that it is the patients themselves who have to carry the risks and 2) the weight they assign to prolongation of life, it is questionable whether patients having the same information as the IRB members would come to an RBR assessment similar to that of IRB members.

6.4 How to close the gap between practice and legal rules

One can question whether patients, from their perspective, will come to the same RBR assessment as IRBs. If this doubt is grounded, one should ask what relevance can be attached to an IRB's statement that the ratio between the risks and the benefits of a study is reasonable. Imagine someone who wants to invest his money and goes to his bank for advice. The bank mentions some funds in which he can safely invest his capital. 'Safely' only means that such an investment will not be too risky. It does not say much, if anything, about the percentage of profit he can expect. If the bank was in the position to say that he could expect reasonable profit, he might conclude that the profit would be at least around the average of comparable investment funds. In our opinion, an IRB's approval of a protocol does not say much more than that participation is relatively safe. Patients cannot conclude that the balance between the risks and the benefits of a study is reasonable for them, simply because the IRB has, as a part of the approval procedure, assessed the RBR ratio. They may conclude that the risks are acceptable and that participation will provide some benefits. However, this is much less than what the legal requirements demand that approval of a study by an IRB denotes. As we have seen, the Dutch law states that an IRB can only approve a research protocol "if it can reasonably be expected that the interest to be served by the research is proportional to the burdens and risks for the research subject". The U.S. Common Rule requires "that risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." Clearly there is a gap between the legal rules and what is actually done by IRBs. We see three possible ways to close this gap. The first is to change the rules and/or to reformulate the tasks of IRBs. In the new formulation IRBs would be required to 1) judge the scientific validity and importance of the research, 2) identify and estimate the diverse risks and benefits, 3) determine whether the risks are acceptable and whether there is potential benefit for the research subjects or future patients and 4) check whether the patient forms are accurate and complete. The main difference between the current regulations and this alternative is that IRBs would no longer be required to determine whether the risks are proportional to the benefits. Only patients themselves would then decide whether, from their particular perspective, the relation between the risks and benefits (both to themselves and to science/society) is reasonable.

This proposal reflects the practice of at least some IRBs.[x] It does not imply a radical change in the work of an IRB; only a recognition of its limits. Nonetheless, we should carefully consider possible objections. The first objection is whether we can expect patients to make a well-informed decision on the reasonableness of the risk/benefit ratio, when even IRB members sometimes indicate that they lack information and do not feel competent to evaluate the diverse risk-benefit issues. As to the lack of information, we

believe that IRBs should be more strict in withholding approval of protocols that do not contain sufficient information about risks and benefits. Patients should not be asked to participate in a trial if an IRB thinks that there is not sufficient information available for them to determine whether there is a balance between risks and benefits. The other issue is whether patients are competent to assess the RBR-ratio, given the fact that even IRB members often doubt their competence in this regard. We do not think that IRB members doubt their competence because they lack experience. IRB members usually are quite experienced. What they mean when expressing doubts about their competence is that they find it difficult to make general, objective statements about the weight of the diverse and incommensurable risks of a study in relation to its also diverse and incommensurable (potential) benefits. They realise that not only does their perspective differ from that of patients, but also that the perspective of* **the** *patient does not exist. Patients' perspectives are usually quite diverse. Using Taylor's terminology, there is not a shared perspective from which an IRB can make the incommensurable for all research subjects commensurable. Patients do not have that problem. They only decide for themselves. They are free to weigh risks and benefits from their own, personal perspective. We want to stress that, even when the legal requirements are brought in line with the current practice, it still remains the task of the IRB to identify and estimate risks and benefits, and to see to it that information provided to patients does not create false impressions about the possible benefits.

A second possible objection to changing the legal requirements is that patients, who are seriously ill and who often have to decide quickly about trial participation, may not be competent to assess the ratio between risks and benefits, especially when it concerns complex trials. We cannot address all the issues involved in determining what exactly is meant by 'competence to consent' and decision making capacity, which criteria one needs to use to assess it, and when to apply these criteria. There is no consensus about these issues in the literature (VanderVeer, 1986; Berghmans, 2000). We limit ourselves to three factors that may influence patients' capacity to decide negatively: the stress caused by the context in which a decision has to be made (lack of alternatives, urgency), the complexity of the decision, and the tendency to overestimate benefits because of hope. These factors already constitute a threat to patients' competence to informed consent under the current regulations. What is relevant to discuss here is whether this threat to patients' competence becomes more serious when patients can no longer assume that the IRB already has assessed the ratio between risks and benefits as being reasonable. On the one hand, we recognise that patients may experience the decision as more complex when they think that they cannot rely on the IRBs judgment on the risk/benefit ratio. On the other hand, the recognition that judgments by IRBs largely reflect the IRBs' shared values and beliefs, might free patients' decisions from illusions. We realise that many patients do not have a clear understanding of their role as research subjects because they lack an understanding of what it means to participate in a study,

confuse research with treatment or see research as 'cutting edge' treatment (Daugherty, 1999; Miller, 2000; Joffe et al., 2001; Cox, 2002). This tendency to blur the boundary between research and treatment may be particularly likely in early clinical trials and when subjects are severely ill (Schaeffer et al., 1996). As is evident from various studies addressing the question of the 'therapeutic misconception' by research subjects (Appelbaum et al., 1982; Appelbaum et al., 1987), many patients in early trials are motivated to participate because they expect therapeutic benefit. However, the 'therapeutic misconception' is probably not only present among patients, but also among investigators (Schaeffer et al, 1996; Appelbaum et al., 1982; Appelbaum et al., 1987; Miller, 2000).

A second way to close the gap between actual practice and legal requirements would be an authoritative (re)interpretation of the rules. In that case a court or another legal institution would state that the legal requirement as to determining the reasonableness of the relation between risks and benefits should be conceived as determining whether the risks are reasonable and whether the research has the potential to benefit the research subjects and/or future patients. This second alternative is different from the first only in strategic terms. The choice between these two options will depend on the nature of a country's legal culture and legal preferences.

There is also a third way forward that we will discuss only briefly. This is to bring the practice of IRBs more in accordance with the literal meaning of the legal rules. A possible step in that direction could be that IRBs enlarge their perspective by taking account of patients' views on the relation between risks and benefits. This could be done in two ways. First, one could require that IRBs also have patients as members.[xi] Stage 1 of our study, involving semi-structured interviews with IRB members about their evaluations of phase II and phase III clinical trial protocols, yielded results that are relevant to this issue, and that suggest an intriguing paradox.[xii] The results indicated that most IRB members would like to receive additional information and education in assessing the RBR of clinical trials, and that most IRB members also believe that additional insight into the experiences and perceptions of patients would help improve the assessment process. However, only about half of the participating IRB members favored having patients as members of IRBs. Thus, a proposal to include patients in an IRB most likely will not be widely accepted. It may be that IRBs find it sufficient to be informed about the experiences and perceptions of patients through nurses and the primary care physicians who are traditionally viewed as representing the interests of the patients on IRBs. It is also conceivable that the discussions within the IRB can supply at least part of the information that is needed. However, our study did not investigate this possibility. A second way for IRBs to enlarge their perspective is to take account of patients' trial experiences. As yet, limited research has been done into these experiences (see e.g. Madsen et al., 2002).

Much can be done to improve the work of IRBs. Above all it is necessary to further develop a common conceptual framework for describing and assessing both risks and benefits. We believe that IRBs should demand that clinical trial protocols contain more precise and reliable information about risks and benefits, and that information provided to patients do not create false impressions about the potential benefits of the research. However, all these measures will not be sufficient to close the gap between the actual practice of IRBs in determining whether the relation between risks and benefits of a research proposal is reasonable, and the legal requirements. We have discussed three possible ways of closing this gap. At this moment we do not know which of this is the best and most feasible way forward. Additional research and discourse is needed to determine which strategy is optimal.

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7 Summary and conclusion

What are the results of this study and how must they be evaluated? The last chapter of the report is divided into three parts. First, we describe in section 7.1 the background of the study, the main research question, and the study design. Second, in section 7.2 we give a summary of the main empirical and empirical-ethical results of the articles in this report. Finally, we draw some conclusions (section 7.3).

7.1 Background and research question

Before summarizing the results of the research, we will recapitulate what we said in the introduction about the background of the research and the central research question. It was clear to us from other studies that not only do IRB members have difficulty identifying the relevant risks and benefits of a particular protocol, they also find it difficult to compare those risks and benefits because (1) the nature, extent and the duration of risks and benefits are often uncertain, (2) the nature of the various risks and benefits is very diverse, and (3) all of the risks accrue to the research subjects, while some of the benefits accrue to future patients and/or to medical science. Moreover, in our opinion the lack of consensus on the content of, and categories and criteria for evaluating the RBR render IRB evaluations unavoidably subjective and intuitive even though they are usually based on long-term clinical experience. The lack of shared categories and criteria makes it difficult to trace and discuss differences of opinion within an IRB, and thereby reduces the chances that the evaluation of the ratio between risks and benefits will play a prominent role in the final decision regarding the ethical acceptability of the research. This is why we decided to set up this research. We also had some intuitions about why assessing the RBR is so difficult which we wanted to examine empirically. Firstly, RBR concerns risks and benefits that have impact on different dimensions of the health or quality of life of the research subject. We inclined to agree with those authors who think that these risks and benefits are incommensurable. The problem of incommensurability is aggravated because the benefits not only accrue to the research subjects, but also to future patients and for medical science. Secondly, the weighing of risks and benefits always takes place within a certain context. Decisions about the RBR of a trial depend on whether there are alternative treatments and on the quality of these alternatives.

The main research question of this study was:

> **What risks and benefits do IRB members identify in Phase II and III cancer clinical trials, how do they estimate and evaluate these risks and benefits, and what is the relationship of the evaluative dimensions of risks and benefits (e.g. divers physical, psychosocial risks and benefits to participating patients) with the RBR assessment and the ethical acceptability of these experiments?What other factors determine these assessments and can IRBs**

assess the heterogeneous and incommensurable risks and benefits? And what does it mean when they cannot?

Experimental treatments in oncology differ from other experimental treatments in that the risks associated with the treatments are usually quite serious. The difficulties in determining the ratio between risks and benefits are therefore more prominent in clinical oncology than in other medical fields. That is the reason why we chose to study the RBR assessment in Phase II and III clinical cancer trials.

In order to answer the main research question of this research, we opted for a study design with four stages in which different research methods were used. These four stages were: (1) semi-structured interviews with 53 IRB members from six research hospitals and specialized cancer centers in the Netherlands, (2) a questionnaire about an evaluation of a Phase II breast cancer clinical trial and a Phase III lung cancer clinical trial administered to 43 and 41 IRB members from those six research hospitals and specialized cancer centers, (3) in-depth interviews with 35 of these IRB members about their evaluations in stage 2, and (4) observation of meetings of two full IRBs while they were discussing the protocols evaluated in stages 2 and 3.

7.2 Summary of the empirical and empirical-ethical results

In this section we summarize the main results of the research described more extensively in the various articles.

1. *What kind of risks and benefits do IRB members identify in Phase II cancer clinical trials in general?*

All of the respondents identified the toxicity and side-effects of treatment, and nearly all the additional burdens associated with trial participation (e.g., frequent visits to the hospital, extra tests) as common risks associated with trial participation. Less self-evident was that 65% of the respondents identified psychosocial risks associated with trial participation. These included uncertainty about what is going to happen, a potential (and false) sense of hope about treatment efficacy, confrontation with the fact that the disease cannot be cured and that the treatment may be of only limited or no direct benefit. Additionally, 20% of the respondents reported a decrease in quality of life as a risk of treatment.
Conversely, 68% of the respondents indicated a number of specific psychological benefits associated with participation in a Phase II trial. These included an increase in the amount of attention and support received from medical and ancillary health-care providers, a sense that there is still something that can be done to actively treat the disease, as well as a personal feeling of being able to fight back against the disease. Approximately one-third of the respondents identified improved quality of life, and one-quarter treatment efficacy as a possible benefit. The potential for developing more effective cancer therapies was rated as the primary benefit to future patients and to the scientific community.

2. *Is the information available in Phase II cancer protocols adequate for evaluating risk/benefit issues? And do IRB members consider themselves competent to make risk/benefit assessments?*

Only a small minority of the respondents (8%) indicated that Phase II protocols typically contain too little information about the types of benefits that might accrue to participating patients. However, between approximately one-quarter and one-half of the respondents reported that frequently there is insufficient information provided about the likelihood, the magnitude and the duration of such benefits. IRB members believed that protocols provide sufficient information about the types of risks involved in Phase II clinical trials. However, a substantial percentage of the respondents indicated that too little information is available regarding the likelihood, seriousness, duration and reversibility of those risks (44%, 36%, 60% and 36% respectively). Almost all of the respondents (90%) indicated that sufficient information is provided regarding the potential importance of the clinical trial for future patients and for medical science.

Between 15% and 34% of the IRB members reported that it was (very) difficult to judge the various risks and benefits associated with Phase II clinical trials, both for participating patients and for future patients and society at large.

3. *How do IRB members evaluate specific risks and benefits for patients participating in Phase II clinical trials, for future cancer patients, and for medical science? Or in other words: How do they weigh risks and benefits against each other, and what is the most decisive factor in this decision?*

Most IRB members do not weigh risks and benefits against each other in a systematic way, but rather try to gain an overall impression (20%), to consider what alternative treatments are available (15%), whether one would be willing to undergo the trial-based treatment oneself or would advise a family member to do so (10%). Seventeen percent of the respondents indicated that they typically leave the decision as to whether the benefits of a trial outweigh the risks to the patients themselves, and 12% reported that it is a task for the IRB as a whole, rather than for himself or herself as individual IRB member.

One-third of the respondents were unable to identify a decisive factor in assessing the risk/benefit ratio in Phase II clinical trials because they themselves did not systematically assess risk and benefits. The issue reported most frequently as being decisive was the potential value of the trial to future patients and to medical science (i.e., the potential of finding a more efficacious treatment) (21%). This was followed by the risks, burdens and inconvenience to participating patients (18%), the expectation that the treatment would be beneficial to the participating patients (16%), and feeling comfortable in proposing the trial-based treatment to patients (11%).

4. *Are there systematic differences in the perceived adequacy of information typically available in Phase II cancer protocols, and the perceived competence to evaluate the scientific and risk/benefit ratio issues of those protocols, due to IRB members' characteristics?*

When comparing oncology specialists with other IRB members (including family physicians), statistically significant differences were observed in: (1) the perceived adequacy of information provided in trial protocols about the likelihood of benefits (100% versus 68%) and risks (89% versus 49%) to patients, and (2) perceived competence in evaluating the toxicity of the treatment (100% vs. 50%), the invasiveness of the treatment (100% versus 55%), the originality of the trial (89% versus 30%), and the place of the trial in relation to previous research (89% versus 34%).

5. *What are the most difficult aspects of assessing the RBR of Phase II and III cancer protocols in general?*

Making RBR decisions without clear criteria and in the face of uncertainty with regard to patient benefits and study rationale were perceived as the two most difficult aspects of the RBR assessment for Phase II and III cancer trials by 62% (for Phase II studies) and 39% (for Phase III studies). A minority mentioned other aspects as well such as: research confronts patients with difficult choices in the face of necessary risks; it is hard to gain a view of all relevant factors; the difficulty of withholding treatment because of placebo.

6. *Is there a need for more information and education to make RBR assessments, and how can RBR assessments be improved? Would participation of lay individuals and patients improve the quality of the assessments?*

Fifty-six percent of the IRB members would like to receive more information and training in assessing the RBR of protocols. Approximately half of the respondents who expressed an interest in more information or training were interested in attending courses or seminars, and one-third reported a need for feedback on trial results and on the experience of patients who participate in trials. Eight percent was interested in reflection on past decisions and an overview of new developments in oncological research. About one-third mentioned still other aspects. The percentages do not total 100% because more than one type of support could be mentioned.

Suggestions were made by IRB members to improve RBR assessments, such as that more information be placed at their disposal, particularly regarding the experiences patients had with participating in trials and their perceptions of the risk and benefits.

7. *What is the effect of background characteristics concerning IRB members' ratings on information to and participation of lay individuals and patients?*

The only significant finding was that fewer oncologists (18%) found that more knowledge and education was necessary in making risk/benefit assessments than did other professionals (62%). Younger IRB members (age < 40) favored *lay participation* in IRBs more than did older members (70% versus 38%). For the other

characteristics no significant relationship was found with respect to lay individuals' membership. The most substantial (although statistically non-significant) difference with respect to letting patients participate on IRBs was that fewer physicians (12%) found patient IRB participation desirable than did other professionals (35%). Relatively new IRB members (those with four or fewer years of experience) were significantly more likely to favor *patient participation* on IRBs than were members with more IRB experience (38% versus 4%). Women rejected the idea of patient IRB participation significantly more often than men (72% versus 4%).

8. *What risks and benefits do IRB members identify in a Phase II breast cancer trial, and how do they estimate and evaluate these risks and benefits?*

Inconvenience

Hospital admission and time investment (travel, waiting, etc.) were rated as the most inconvenient aspects of trial participation: 93% and 72% of the IRB members estimated these aspects as 'very inconvenient' orrather 'rather inconvenient,' Additional examinations and extra control visits were rated by 73% and 56% of the respondents as 'very inconvenient' or'rather inconvenient.'

Toxicity

There was broad agreement among IRB members on the expected toxicity of the treatment: hair loss, diarrhea, nausea, vomiting, fatigue and organ toxicity were estimated by most IRB members as 'very likely' to 'rather likely.' Additional toxicities expected by IRB members to be 'very likely' or 'rather likely' were: mucositis, infection, fertility problems/damage to offspring, bleeding, change of skin color, high blood pressure, tremors, painful hands and feet, stomatitis, hematuria, genetic disturbances, and rejection of donor bone marrow.

Most respondents rated these toxic effects as 'rather severe' to 'life threatening,' expected hair loss and fatigue to last for some months to years, and 30% and 44%, respectively, expected organ toxicity and cognitive neurological problems to last for some months to years. Although hair loss, diarrhea, and nausea and vomiting were expected to be reversible, fatigue and organ toxicity were typically not. Also, half of the respondents expected cognitive/neurological problems to be 'irreversible' or 'sometimes irreversible.' Although most expected some toxic effects to be amenable to treatment, for hair loss and fatigue this was not the case. Furthermore, half of the IRB members expected organ toxicity and cognitive/neurological problems, and more than one-third expected other, non-treatable, toxicity. Only a small percentage of respondents did not know how to estimate the likelihood, severity, duration, reversibility and amenability to treatment of toxic effects.

Psychosocial distress

Ninety-three percent of the IRB members believed trial participation would entail psychological distress for the patient beyond that caused by the illness itself. Approximately 50% expected patients to experience depression, 79% stress, and 88% uncertainty as a result of trial participation. Other forms of psychosocial

distress, such as loneliness, donor dependence, and fear were identified by 16% of the IRB members. Most respondents rated depression, stress, and uncertainty as 'rather severe' or 'very severe.' More than one-third expected depression, stress and other manifestations of psychological distress to last for some months to years, while two-thirds expected uncertainty to last that long or longer. Most IRB members were able to estimate the likelihood, severity and duration of the psychological burden. Seventy-two percent of respondents believed trial participation to be a social burden for the patient. Two-thirds expected a strain on relationships with partners and on other social contacts. Seven percent also mentioned long periods of illness or a strain on the patient's professional life as expected stressors. Most IRB members rated the extra strain on the relationship with partners and other social contacts to be 'rather severe' or 'severe,' while about half expected this to last for some months to years.

Benefits to participating patients

Forty percent of the respondents expected tumor remission and 35% a longer symptom-free period to be 'rather likely' or 'very likely.' Only a minority of IRB members expected that other benefits would accrue to patients (e.g., 16% longer overall survival, 14% less toxicity, 7% less pain, and 7% a better quality of life). Two-thirds of the respondents believed that trial participation would provide patients with hope. The majority of IRB members expected tumor remission, prolongation of life, a longer symptom-free period, other toxicities, and hope to last for some months to years; other potential benefits such as less toxicity than an alternative treatment (or no treatment), less pain, and a better quality of life, were expected to last only several days or weeks. Approximately two-thirds of the respondents evaluated the benefits to patients as 'very important' or 'rather important.'

Benefits to future patients and science

Sixty-eight percent of the IRB members were unable to estimate how many patients in the Netherlands would benefit annually from the experimental treatment, should it prove effective. Most members rated the clinical trial as 'rather important' to 'very important.'

Evaluation of risks and benefits.

The possible risks and benefits of the experimental treatment to the patients were rated as 'rather important' or 'very important' by 63% and 91% of the IRB members respectively. The importance of the trial to future patients and science was rated as 'high' by 23% and 10%, respectively. Although nearly all (98%) of the respondents rated toxicity as the most important risk of the trial treatment, they also evaluated the inconveniences and the psychological burden to patients as 'very important' or 'rather important' in their risk/benefit assessment of the trial.

9. *What is the IRB members' assessment of the risk/benefit ratio and the ethical acceptability of the protocol? Is there a relationship between the various risks and benefits and the assessment of the RBR, and the ethical acceptability of the protocol?*

Final assessment of the risk/benefit ratio (RBR) and the ethical acceptability of the research

Thirty percent of the IRB members believed that the risks of the protocol outweighed the benefits, 21% believed that the benefits outweighed the risks, and 35% assigned approximately equivalent weights to the risks and benefits. Thirty-seven percent of the IRB members would approve the protocol and 44% would recommend approval following revision. Although 44% of the IRB members believed that the risks outweighed the benefits or were unable to evaluate the risk/benefit ratio, only 18% would reject the protocol or could not judge its ethical acceptability. There was a significant relationship between the assessment of the RBR and of the ethical acceptability of the trial.

Differences in overall assessment of the RBR and the ethical acceptability as a function of ratings of specific risks and benefits

There were several significant relationships between the assessment of (aspects of) particular risks and benefits and the RBR assessment, especially between the assessment of the duration of several risks and RBR assessment. Inconvenience and benefits to participating patients had no or only a few significant relationships with this assessment. Duration and importance of tumor remission, and duration of a symptom-free period were significantly related to both the assessment of the RBR and the ethical acceptability of the trial. IRB members who believed the risks to outweigh the benefits, believed toxicity and cognitive neurological problems to be significantly more likely, the duration of hair loss, diarrhoea, nausea, vomiting and toxicity to be longer, cognitive neurological problems to be more often irreversible, and the extra burden on other social contacts to be more severe and to last longer.

10. *Are there systematic differences in assessment of the risk/benefit ratio and the ethical acceptability of the protocol due to IRB members' characteristics?*

Physicians did not differ significantly from other professionals in the assessment of the risk/benefit ratio and of the ethical acceptability of the protocol. This was also true for oncologists compared to other IRB members. Nurses, however, differed significantly from other IRB members in their assessment of the ethical acceptability of the protocol.

Relatively new IRB members (membership of four years or less) were significantly more likely to approve the protocol, or recommend approval after revision, than members who had a longer association with an IRB. Length of IRB membership did not correlate significantly with the RBR assessment of the protocol. Some significant relationships were found between age and gender and the assessment of the RBR or with the ethical acceptability of the trial.

When including all IRB members' characteristics in a multiple logistic regression analysis, only gender was associated significantly with the assessment of

the ethical acceptability of the trial. Female members were significantly more likely to reject the protocol or to recommend approval after revision than males (p <. 014). There were no significant relationships found in a multiple logistic regression for all IRB members' characteristics and the RBR assessment.

11. *Can IRBs assess the heterogeneous and incommensurable risks and benefits of research protocols?*

The heterogeneous and incommensurable nature of both the risks and the benefits of an experiment make an *objective* assessment (we mean an assessment from an objective, scientific point of view) of its RBR impossible. In assessing the RBR of a trial, IRBs need to agree upon the relative weight of specific risks and benefits. However, one cannot assign weight to risks and benefits without referring to certain extra-scientific, moral background values. Thus, in order to reach agreement on the RBR, IRB members need to have a certain consensus on these background values and their relative order. Other IRBs or patients who do not share this view on values and order may come to a different judgment about the reasonableness of risks in relation to benefits.

In our view IRBs cannot meet the normative expectations implied in current laws and rules of diverse countries. The problem of the incommensurability of risks and benefits renders them unable to determine *objectively* whether the relation between risks and benefits is reasonable. What they actually do is ensuring that a proposed experiment does not present unreasonable/unacceptable risks for research subjects and that the study has the potential to benefit them and/or future patients.

12. **Given that IRBs can or cannot assess the heterogeneous and incommensurable risks and benefits of research protocols, how does this affect the policy and practice of reviewing experimental medical treatments?**

As said before, in our view the actual practice of IRBs in reviewing a research project does not meet the legal requirements. There are several ways to close the gap between legal demands and actual practice. First, adjusting the legal rules to the actual practice by reformulating the tasks of IRBs. In the revised form the main task of an IRB should be 1) to judge the scientific validity and importance of the research, 2) to identify and estimate the diverse risks and benefits, 3) to determine whether the risks are reasonable and whether the research has the potential to benefit the research subjects and/or future patients and 4) to check the correctness and completeness of the patient forms. In this formulation IRBs are not required to make a complete and comprehensive judgement about the reasonableness of the relation between risks and benefits. That judgment is left to the potential research subjects. This implies the recognition that only patients themselves should decide whether, from their particular perspective, the relation between the risks and the benefits is reasonable. It does not imply a radical change in the work of an IRB, only recognition of its limits. A second way to close the gap between actual practice and legal rules would be an authoritative (re)interpretation of the rules. In that case a

court or another legal institution would specify ‘reasonableness’ in order to determine whether the risks are in fact reasonable and whether the research in fact has the potential to benefit the research subjects and/or future patients. A third way is to improve the actual practice of IRBs in such a way that it accords more with the rules. A possible step in that direction could be that IRBs enlarge their perspective by taking account of patients’ views on the relation between risks and benefits. These three ways were presented as possibilities to close the gap between the actual practice of IRBs in determining whether the relation between risks and benefits of a research proposal is reasonable, and the legal rules for making these assessments.

As said before (see Introduction) not all sub-research questions of the study were answered in the articles included in this report. A manuscript about the assessment of the risks and benefits of a specific Phase III cancer trial (*The evaluation of the risk and benefits of Phase II cancer clinical trials by Institutional Review Board (IRB) members: A case study*) is in preparation. This is also true for a manuscript about the considerations of IRB members behind their assessments of the RBR and the ethical acceptability, and for a manuscript focused on the deliberations in two IRBs about the specific protocols that had been evaluated by the individual IRB members in stage II of this study.

7.3 Conclusions

In this last section we will present some general conclusions from our study. We start with a brief discussion and conclusion with respect to the suitability of the conceptual model used in this study for describing and explaining the RBR assessment of research protocols by IRB members. We end with a few additional conclusions.The aims of the research were:

(6) to provide insight into the impact that judgments on the diverse evaluative dimensions of experimental treatments (scientific importance, side effects, length of survival, quantity of tumor remissions, symptom-free period etc.) have on the final decision about the acceptability of these experiments;
(7) to provide insight into the factors that play a role in balancing the heterogeneous and incommensurable burdens and benefits of experimental treatments in oncology and that could explain the possible differences in evaluations between members of an IRB;
(8) to contribute to increasing the transparency and the justifiability of judgments by IRBs about the proportionality of benefits and burdens of experimental treatments in oncology and thereby to enable IRBs to monitor the consistency in their judgments and decisions with regard to different research protocols;
(9) to provide insight into what from an ethical point of view should be the relation between the principle of respect for autonomy – the liberty of research subjects to form, on the basis of their personal preferences and values, their own judgment about the proportionality of benefits and burdens

of participating in a research project – and the principle of non-maleficence that obligates the IRBs to make a general judgment of the ethical acceptability of the research;

(10) to contribute to insight into the feasibility of the legal obligation of IRBs in the Netherlands to determine the proportionality of the ratio between benefits and burdens of medical experiments with humans.

The conceptual model and the RBR assessments by IRB members

The process of the RBR assessment

In our conceptual model the RBR assessment consists of different processes, namely primary and secondary appraisal (i.c. the identification, estimation and evaluation of the risks and benefits) and the coping (=decision making) itself (i.c. the weighing of risks and benefits, and the emotion-regulating processes). Also a diverse range of risks and benefits are distinguished such as physical, psychological and social risks and benefits of humane research. The results of this study show that the conceptual framework (the distinction between the various processes and the different categories and dimensions of risks and benefits) is partly adequate (cf articles 1 and 3). IRB members do identify various physical, psychological and social risks, and physical and psychological benefits of participation in Phase II cancer trials for participating patients, and benefits for future patients and medical science. They were able to identify and estimate risks and benefits for participating patients according to pregiven evaluative dimensions (e.g. the likelihood, duration etc.), and to evaluate benefits for medical science; the benefits to future patients were more difficult to evaluate (cf article 3). However, although IRB members can answer closed questions in order to identify, estimate and evaluate risks and benefits, it is questionable whether this is actually done in this way. First, the pregiven risk/ benefit issues inevitably influenced the way they evaluated the protocols. Second, only a minority of IRB members assessed the RBR in a systematic way, as the semi-structured interview learned. Therefore the conclusion must be that identification, estimation and evaluation (according to the model - the judgment and evaluation processes), are adequately conceptualized only when there is an ideal study situation in which IRB members are forced to think about risks and benefits according to extensive survey questions. In normal life, where such a laboratory situation is lacking, these processes do not take place so systematically, as the semi-structured interview shows. As a rule the RBR assessment is a global decision-making process. The distinction in the model between the different processes is probably adequate only when ‘ideal’ evaluations take place according to pregiven lists of evaluating dimensions.

Our model also distinguishes between different decision strategies. Some of these processes, such as information search processes and interactions with others, will probably take place during the collective decision making in IRB meetings. However, individual IRB members’ examples of these decision-making strategies were also found in the empirical data. For example, most IRB members do not weigh risks and benefits in a systematic manner, as was

already said; rather, they relied on global impressions or preferred to leave such matters to the IRB as a whole or to the patients. Weighing of risks and benefits is only one decision-making strategy (this can be categorized as rational weighing of advantages and disadvantages). Other strategies are emotion-regulation processes such as leaving the decision to the patients or the IRB as a whole. Also, IRB members sometimes try to imagine that they themselves or their loved ones were subjects in the trial they are evaluating (mental imaging). Some say this was the only way they were able to come to a decision on the RBR. Furthermore, a possible explanation of the fact that a number of IRB members could not make an RBR assessment (because they lacked criteria) might be that the usual way of making decisions – by mental imaging and anticipating behavior – is sometimes inappropriate. This is probably due to the fact that IRB members need to decide for others (e.g. the participating patients in the trial) and not for themselves.

We can conclude that the different decision-making strategies that were conceptualized in the model are reflected in the empirical data.

Determining factors

The model mentions several factors that may determine IRB members' assessment of the RBR of Phase II and III trials. These factors might determine the judging and evaluation processes as well as the actual decision making. Only part of these factors was actually included in this study. They may be categorized into internal (or intermediate) and external factors. Internal factors are factors that determine the evaluation and decision-making process, but are part of this process itself, such as the evaluation of the different evaluative dimensions of the risks and benefits. External factors are factors that determine the evaluation and decision-making process from the outside (independent factors).

Internal factors

There were several significant relationships between the assessment of (aspects of) particular risks and the benefits, and the RBR assessment of the Phase II cancer trial. This was especially so for the assessment of the duration of several risks and the RBR assessment (cf article 3). IRB members who believed the risks to outweigh the benefits, further believed toxicity and cognitive neurological problems to be significantly more likely, the duration of hair loss, diarrhea, nausea, vomiting and toxicity to be longer, cognitive neurological problems to be more often irreversible, and the extra burden on other social contacts to be more severe and longer lasting. Of the benefits only duration and importance of tumor remission, and duration of a symptom-free period were significantly related to the assessment of the RBR.

Duration and importance of tumor remission, and duration of a symptom-free period were also significantly related to the assessment of the ethical acceptability of the trial; other benefits to participating patients or (aspects of) the inconvenience and risks were not.

External factors

In the evaluation of Phase II studies in general (article 1), we found indications regarding the influence of *the perceived adequacy of the information* typically available in Phase II protocol, and *the perceived competence* of IRB members to make risk/benefit assessments. A substantial percentage of IRB members (between 25%-60%) reported that too little information was available about more specific issues such as the likelihood, magnitude and duration of such risks and benefits. The lack of detail provided in protocols may explain, at least in part, the finding that one-third of IRB members do not make a risk/benefit calculation at all, and that 17% leave such matters up to patients. Also, a substantial minority of IRB members (ranging from 15% to 40%) reported feeling less than fully competent to evaluate the risks and benefits associated with Phase II trials and the scientific details of these trials. We did not inquire whether in this case the relationship of the perceived competence to make risk/benefit assessments and the RBR assessment is significant; this will be studied in a future paper. Also the *lack of decision-making criteria* plays a role. A substantial number of IRB members reported that they lack criteria to make risk/benefit assessments (cf article 2).

Finally, several* sociodemographic and professional status characteristics *were, as we have seen, found to be significantly related to the RBR assessment and the assessment of ethical acceptability. The IRB members' age had a significant relationship with the outcome of the RBR assessment of the specific Phase II cancer trial. In a multivariate analysis, however, the age effect disappeared. Professional status (nurse vs. non-nurse), length of membership, age and gender had significant relationships with the* outcome *of the assessment of the ethical acceptability of the specific Phase II cancer trial. In a multivariate analysis including all of the IRB member's sociodemographic and professional characteristics, only gender was found to be associated significantly, with female members being significantly more likely to reject the protocol or recommend approval after revision than males.

The conclusion is that several of the factors in the model are associated significantly with the RBR assessment, or there were indications for such association. Not all relevant factors mentioned in the model were studied so far; others will be the subject of future study.

Impact of the evaluative dimensions of experimental treatments on the assessment of their ethical acceptability

The first aim of the study was to provide insight into the impact that judgments on the diverse evaluative dimensions of experimental treatments (scientific importance, side effects, length of survival, quantity of tumor remissions, symptom-free period etc.) have on the final decision about the acceptability of these experiments.

We have seen that several evaluative dimensions of risk and benefits are significantly associated with the RBR assessment. The duration of certain forms of toxicity and the duration and importance of a few benefits (tumor remission and

symptom-free period) to participating patients have impact on *the RBR assessment* of the Phase II breast cancer trial. IRB members who believed the risks to outweigh the benefits, believed toxicity and cognitive neurological problems to be significantly more likely, the duration of hair loss, diarrhea, nausea, vomiting and toxicity to be longer, cognitive neurological problems to be more often irreversible, and the extra burden on other social contacts to be more severe and of longer duration. Of the benefits only duration and importance of tumor remission, and duration of a symptom-free period were significantly related to the assessment of the RBR.

> ***However only the duration and importance of tumor remission and symptom-free period (benefits to participating patients) have impact*** **on the assessment of the ethical acceptability** ***of the trial. We cannot say which of these evaluative dimensions of the risks and benefits to participating patients were most central to the RBR assessment, because our data did not allow us to perform the necessary analysis (a multivariate analysis). According to IRB members (and as we expected) the benefits to future patients and medical science are less important in the RBR assessment of ethical acceptability. We did not study however whether there was a significant relationship between the evaluation of the benefits to future patients and medical science and the assessment of the ethical acceptability of the trial.***

So, only some evaluative dimensions of tumor remission and a symptom-free period were significantly related to the assessment of the *ethical acceptability* of the breast cancer trial; other benefits to participating patients or (aspects of) the inconvenience and risks were not. This means that tumor remission and a symptom-free period are the benefits to participating patients that are most important for IRB members' assessments of the ethical acceptability of the trial. These are more important than the risks to participating patients, and also more important (as we expected) than the benefits to future patients and medical science. This is somewhat disconcerting recognizing that most patients participate in trials because they hope for a treatment effect in terms of prolongation of life (Miller, 2000).

Factors that determine the RBR assessment

The second aim of the study was to provide insight into the factors that play a role in balancing the heterogeneous and incommensurable burdens and benefits of experimental treatments in oncology and that could explain the possible differences in evaluations between members of an IRB. We have seen that several factors play a role in balancing the risks and benefits of these treatments. As said before, in our empirical studies we found that (or found indications that) these factors are: identifications, estimations and evaluations of risks and benefits, the perceived adequacy of the information typically available in Phase II protocols, the perceived competence of IRB members to make risk/benefit assessments, lack of decision-making criteria to make these assessments, and several sociodemographic and professional status characteristics. As noted, not all relevant factors that play a role according to the literature were studied in the articles in this report.

Transparency and justifiability of judgments by IRB members and IRBs

The third aim of this study was to contribute to increasing the transparency, and the justifiability of judgments by IRBs about the proportionality of benefits and burdens of experimental treatments in oncology, and thereby to enable IRBs to monitor the consistency in their judgments and decisions in regard to different research protocols. With regard to this aim we developed our conceptual model. While the model can serve as an aid in making assessments, its concepts and can also be used for articulating and justifying the actual assessments, both of IRBs and individual IRB members. If IRBs were to use the framework for a detailed description of their assessments and decisions in the minutes of their meetings, they would avail themselves of an instrument to monitor the consistency in their judgments and decisions in regard to different research protocols. Forthcoming papers will further contribute to increasing the transparency and justifiability of RBR assessments of Phase II and III cancer studies by IRB members and IRBs.

Relation between the principles of respect for autonomy and of non-maleficence and the feasibility of the legal requirement for IRBs to assess RBR

We take the last two aims together. The fourth aim of the research was to provide insight into what, from an ethical point of view, should be the relation between the principle of respect for autonomy – the liberty of research subjects to form, on the basis of their personal preferences and values, their own judgment about the proportionality of benefits and burdens of participating in a research – and the principle of non-maleficence that obliges IRBs to protect research subjects against unnecessary and unreasonable burdens and risks. The fifth and last aim was to contribute to insight into the feasibility of the legal obligation of IRBs in the Netherlands to determine the proportionality of the ratio between benefits and burdens of medical experiments with humans. In many countries RBR assessments are regarded as an essential instrument for the protection of research subjects. The empirical results suggest that it is difficult or sometimes even impossible for IRB member to make an RBR assessment. The philosophical analysis of the incommensurability of risks and benefits explains what one means when saying that it is not possible to make an RBR assessment: it is impossible to assess the RBR in an *objective*, scientific way; non-scientific value judgments will always be involved. This is probably also the reason why some IRBs are inclined to refer to the principle of respect for autonomy and leave the assessment of RBR to the potential research subjects. What has to be reconsidered is not the relationship between the principle of respect for autonomy and the principle of non-maleficience. In our view the principle of non-maleficence still outranks that of respect for autonomy. What has to

be reconsidered is the scope of that principle: whether or not the requirement that IRBs make an RBR assessment should be maintained.

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Notes

[i] The various legal texts dealing with the requirement of correlation between risks and benefits differ as to the standard of comparison. While some demand a "reasonable" relationship (See Guideline 8 of the Council for International Organizations of Medical Science (CIOMS) or "not disproportionate" (See Article 16(ii) of the Convention on Human Rights and Biomedicine; and Article 6 of the draft Protocol thereto), others require that the potential benefits "justify" (See Section 2.2 of the Guideline E6 of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; CIOMS Guideline 8; Section 3 of the Nuremberg Code; Article 3(2)(a) of Directive 2001/20/EC of the European Commission), "exceed" (Section 6 of the Nuremberg Code demands that the risks do not exceed "the humanitarian importance of the problem to be solved".), or "outweigh[s]" (See Paragraph 18 of the Declaration of Helsinki) the benefits. Some regulations point at the different evaluation of possible risks and benefits for the research subject depending on whether the person is ill and in need of treatment or not (See Paragraph 18 of the Declaration of Helsinki; CIOMS Guideline 8; Article 6 of the draft Protocol to the Convention on Human Rights and Biomedicine).

[ii] See e.g. Martin et al. (1995); Meslin, 1989; Levine, 1978; King, 2000.

[iii] Martin et al. (1995) are, as far as we know, the first authors to speak of the incommensurability of risks and benefits.

[iv] Important work for developing a conceptual framework to describe risks and benefits has already been done by Meslin (1989), Levine (1978) and King (2000).

[v] See for the concept of covering value: Chang R. Introduction in Chang R (ed.), *Incommensurability, Incomparability, and Practical Reason*. Cambridge, Mass./London: Harvard University Press, 1997:5.

[vi] We do not regard diversity as such between IRBs in RBR-assessments as a problem. Here we agree with Edwards et al. (2004) who state that some inconsistencies are bad because they are due to irrationality, carelessness, the operation of conflicts of conflicting interests, or power struggles within committees. But others are not. They argue that particular inconsistencies should be tolerated, or even embraced as positively valuable, in that they arise out of meritorious features of the research ethics review process. We think that inconsistencies between IRBs will persist even when all IRBs use the same conceptual framework for identifying and describing risks and benefits.

[vii] Prentice ED & Gordon BG, Institutional Review Board Assessment of Risks and Benefits Associated with Research. http://onlineethics.org/reseth/nbac/hprentice.html

[viii] See: Van Luijn, H.E.M., Musschenga, A.W., Keus, R.B. & Aaronson, N.K. (2005). The evaluation of phase II and III cancer clinical trials by Institutional Review Board (IRB) members. Submitted to *Social Science and Medicine.*

[ix] See: Van Luijn, H.E.M., Aaronson, NK., Keus, R.B. & Musschenga, A.W. (2005). The evaluation of the risks and benefits of phase II cancer clinical trials by Institutional Review Board (IRB) members: A case study. Submitted to the *Journal of Medical Ethics.*

[x] One of the respondents in the research by Churchill et al. (2003) stated: "Our IRB usually doesn't look at benefit because you can't assume a benefit, what you have to assume is that it's safe, that it's not going to hurt the patient. And if you get a benefit out of it, well that's a plus."

[xi] This proposal is similar to the 'practical solution' suggested by Martin et al. (1995:9). They propose to invite potential subjects, individually or as a community, to provide a judgment regarding the acceptability of specified risks in relation to the potential benefits.

[xii] See: Van Luijn et al., ref. 8.